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The study purpose was to develop an understanding of race/ethnic disparities in breast cancer survival, with an emphasis on hormone receptor differences. A cohort of 924 breast cancer patients was followed (median 10.0 years). Clinicopathologic and survival data were abstracted from medical records and our institutional and SEER Tumor Registries. Detailed comorbidity data was gathered.
Breast cancer estrogen receptor (ER) status measured in the continuous scale did not carry more predictive information than ER status dichotomized at 10 femtomoles/mg (standard) in predicting cancer progression/recurrence and survival.
The association between ER and progression/recurrence and survival did not differ between Black and Whites.
Comorbidity was an important determinant of survival. Adverse comorbidities occur significantly more in Blacks compared to Whites and explained important amounts of survival disparity.
Adverse presenting symptoms were an important independent predictor of reduced survival. Black patients tended to have more adverse symptoms, and they explained a small amount of survival disparity.
The findings indicate that current dichotomous methods of evaluating ER are appropriate. Comorbidity/symptoms data might be useful in identifying susceptible patients requiring increased monitoring, more aggressive treatment and management of comorbidities. This is expected to lead to improved survival in general and the reduction of disparity.

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INTRODUCTION

African American breast cancer patients have worse survival than their White counterparts, and the reasons for this disparity are not completely understood [1-9]. A general purpose of this study was to develop insight into the causes of the African American disparity in breast cancer survival. Tumor estrogen receptor (ER) and progesterone receptor (PR) positivity are recognized to be important protective prognostic factors in breast cancer [10-13]. Numerous studies have established that African Americans are more likely than Whites to have ER-negative tumors [9,14-19]. The specific initial purposes of this study were to evaluate whether breast tumor hormone receptor positivity evaluated in a continuous scale cared more prognostic information than a simple dichotomous categorization and whether the effect differed by race/ethnicity.

As our *Hormone Receptors & Breast Cancer Prognosis Study* was being initiated, results from another one of our studies indicated that comorbidity and symptoms have an important impact on lung cancer survival and explain a considerable amount of disparities in lung cancer outcomes [20-23]. We incorporated an exhaustive comorbidity/symptoms inventory developed in our lung cancer research into the data abstraction of the *Hormone Receptors & Breast Cancer Prognosis Study*. Numerous studies have found that comorbidity is an independent predictor of survival in breast cancer patients [24-28]. And, although it has been shown that the Charlson Comorbidity Index is similarly predictive of survival in Black and White breast cancer patients [29], it is unclear as to whether differences in comorbidity distribution exist, whether comorbidity explains race/ethnic disparity and whether measurement of comorbidity needs to be optimized to evaluate disparity. The detailed comorbidity/symptoms data that were added to this study were intended to enhance the *Hormone Receptors & Breast Cancer Survival Study* by making possible:
(1) improved adjustment of multivariate models evaluating hormone receptor effects;
(2) evaluation of the associations between comorbidity and hormone receptor status,
(3) evaluation of the associations between comorbidity/symptoms and breast cancer outcomes, including receipt of treatment, breast cancer recurrence/progression, and survival, and
(4) identification of methodologic weaknesses in existing comorbidity measurement protocols for studying disparities in cancer survival.

BODY

METHODS

The Study Setting

The Henry Ford Health System (HFHS) is a large, vertically integrated, nonprofit medical care system that annually cares for more than 500,000 people, approximately 30 percent of whom are African American. In 1997, the HFHS patient population distribution in 10 age, 2 race and 2 gender categories (40 strata) differed from the Metropolitan Detroit (Wayne, Oakland and Macomb counties, 1990 census) distribution by 5.3 percent or less in all strata. These observations suggest that the HFHS patient population is representative of the community it serves.

The HFHS Tumor Registry is American College of Surgeons, Commission on Cancer, certified and has an information exchange agreement with the Metropolitan Detroit Surveillance Epidemiology and End Results (SEER) Registry.

Study Design

A cohort of breast cancer patients (N = 924, 1985-1990) was identified from the Henry Ford Health System Tumor Registry. Hormone receptor data, clinicopathologic data including comorbidity/symptoms data, and survival data were abstracted from hard copy laboratory records obtained from the HFHS Department of Clinical Biochemistry, from hard copy patient files, and from the HFHS and Metropolitan Detroit Surveillance Epidemiology and End Results (SEER) Tumor Registries. Cause of death data was obtained from the Michigan Death Tapes. Estrogen and progesterone hormone receptor status was assayed by a single charcoal-dextran method and reported in the continuous scale. Socioeconomic status (SES) was estimated by area-based socioeconomic measures from patients' addresses and 1990 census data at the block group level, and included median household income, proportion living below the poverty level, and proportion not completing grade 12 or higher. Comorbidity data were collected from medical records from three years prior to index breast cancer diagnosis up until first breast cancer treatment or six months post-diagnosis, if no treatment was administered. The Charlson Comorbidity Index was prepared as described by Charlson et al [30].

Statistical Analysis

Cancer stage and histotypes were analyzed according to American Joint Committee on Cancer (AJCC) tumor-node-metastasis (TNM) [31] (0 = carcinoma in situ (CIS), and stages I, II, III & IV) and World Health Organization histologic categories [32]. The association between relatively higher versus lower stage across the stage levels I through IV, excluding unstaged disease, was studied

using ordinal logistic regression [33]. Standard logistic regression was used to study associations between predictors and dichotomous outcomes.

Univariate and multivariate survival analyses were carried out using Kaplan Meier, life table and Cox proportional hazards regression analyses [34,35]. Modeling proceeded from univariate to multivariate and preparation of parsimonious multivariable regression models was guided by *a priori* considerations [36] and was aided by backward stepwise elimination. Regarding the association between comorbidities/symptoms and survival, a large number of comparisons were made. Although no formal statistical method was used to correct for multiple comparisons, bootstrap estimates of Cox model hazard ratios and 95 percent confidence intervals (95% CI) were prepared to develop a sense of which associations should be interpreted with caution [37].

The receiver operator characteristic area under the curve (ROC AUC) and the c statistic were used to measure the predictive, discriminatory power of logistic and Cox models [33,38], respectively. The c statistic is analogous to the ROC AUC and both statistics can be thought of as follows: Considering all possible combinations of informative (non-tied) paired individuals under study with differing outcomes (case vs. control, longer vs. shorter survivor), the ROC AUC and c statistic represent the proportion for which the regression model correctly predicts the outcome status or survival order [33,38].

The adjusted R^2 statistic was used to describe the proportion of survival variation explained by predictor variables in Cox proportional hazards models [39,40]. In linear regression, the R^2 statistic describes the amount of variance in the dependent variable that is explained by the predictor variable(s). Although, not completely analogous, the same equation used to calculate R^2 in linear regression, $R^2 = 1 - \exp(-G^2/n)$, where G^2 is the likelihood ratio chi-square statistic, can be applied to Cox models in survival analysis [39,40]. The use of R^2 to evaluate goodness-of-fit has been criticized [41-43] but these criticisms do not apply to the use of R^2 as a measure of explained risk [44-46].

Alpha error was set at 0.05 and all reported p-values are two-sided. Stata 7.0 (Stata Corporation, College Station, TX) software was used to prepare statistics.

RESULTS

Study population

The study population consisted of 924 individuals: 69.4% White, 28.5% Black, and 2.2% unknown. The distributions of baseline characteristics and selected variables by race/ethnicity are presented in Table 1. Blacks had significantly lower SES as measured by median household income, poverty level or education (all three rank sum test $p<0.001$; Table 1 & Figure 1, 2 & 3). The ages of pre-menopausal (<50 years) Black and White patients was similar, but of post-menopausal patients, Blacks on average were older than their White counterparts. Highly significantly more Blacks were living without a spouse. Blacks on average were diagnosed with at a higher stage (odds ratio (OR) $_{\text{III \& IV vs. I \& II}}$ = 1.58, 95% CI 1.08, 2.31; p = 0.02)

Table 1. Characteristics of study population, by race/ethnicity

	Black n = 241 (28.9%)	White n = 592 (71.1%)	p-value *
Age (mean)			
Pre-menopausal	42.4 years	42.2 years	$p_{tt} = 0.85$
Post-menopausal	66.7 years	64.7 years	$p_{tt} = 0.04$
Pre-menopausal	21.9%	28.3%	
Post-menopausal	78.1%	71.7%	$P_e = 0.05$
Marital status (% spouseless)	55.7%	37.3%	$P_e < 0.001$
Socioeconomic status - BGMHI	$31,054	$59,558	$p_{tt} < 0.001$
Stage (n (%))			
CIS	7 (2.9%)	23 (3.9%)	
I	68 (28.2%)	217 (36.7%)	
II	114 (47.3%)	264 (44.6%)	
III	34 (14.1%)	57 (9.6%)	
IV	18 (7.5%)	31 (5.2%)	$p_{trend} < 0.01$
Estrogen receptor (ER) (% +) (dichotomized at 10 femtomoles/mg)	72.9%	78.8%	$P_e = 0.13$
logER (continuous)	3.80	3.90	$p_{tt} = 0.54$
Progesterone receptor (PR) (% +) (dichotomized at 10 femtomoles/mg)	84.7%	88.6%	$P_e = 0.33$
Adverse comorbidity † count			
Mean, median, range	2.48, 2, 0-10	1.83, 1, 0-13	
Adverse comorbidity count (n (%))			
0	34 (13.6%)	207 (34.7%)	
1	66 (26.4%)	134 (22.5%)	
2	60 (24.0%)	86 (14.4%)	
3	34 (13.6%)	64 (10.7%)	
4-5	29 (11.6%)	69 (11.6%)	
6-13	27 (10.8%)	37 (6.2%)	$p_{trend} < 0.001$
Adverse symptoms † count			
Mean, median, range	0.55, 0, 0-5	0.49, 0, 0-6	
Adverse symptoms count (n (%))			
0	158 (63.5%)	412 (69.1%)	
1	59 (23.7%)	120 (20.1%)	
2	23 (9.2%)	35 (5.9%)	
3 to 6	9 (3.6%)	29 4.9%)	$p_{trend} = 0.13$

Abbreviations: BGMHI, block group median household income; CIS, carcinoma *in situ*; ER, estrogen receptor; n, subsample number or count; PR, progesterone receptor.

* p_{tt} = t-test p-value; p_{trend} = nonparametric trend p-value; p_e Fisher's exact test p-value.

† Adverse comorbidities & symptoms are described in Tables 5 & 10, respectively.

Figure 1. Distribution of study population by block group median household income, stratified by race/ethnicity

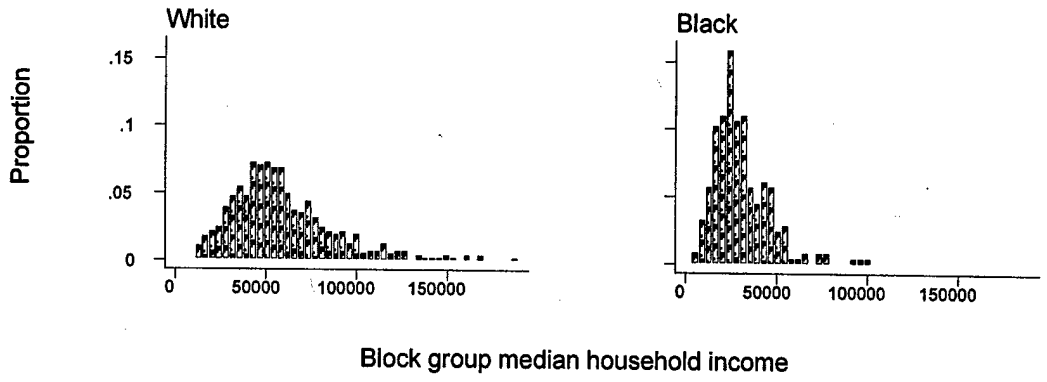


Figure 2. Distribution of study population by percent in block groups with education below grade 12, stratified by race/ethnicity

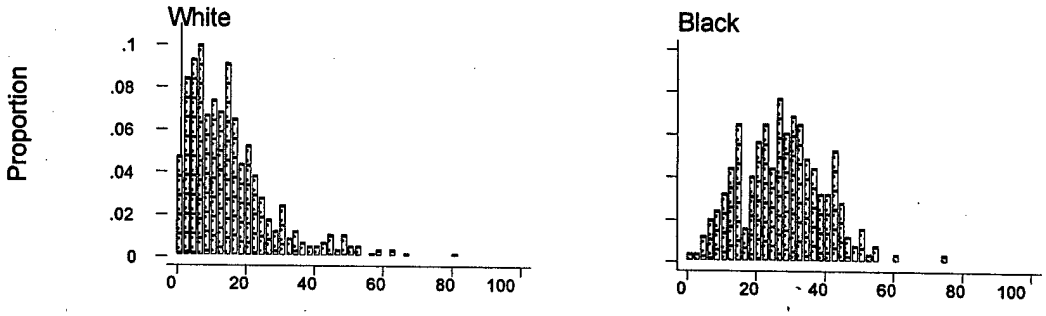
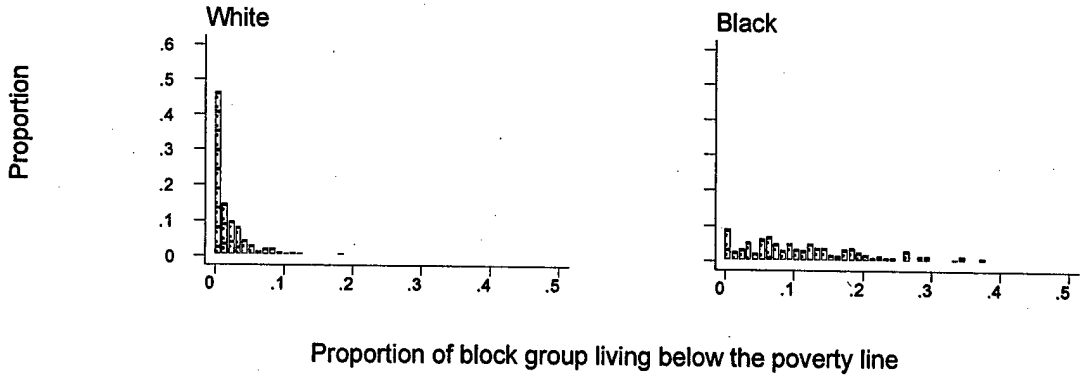
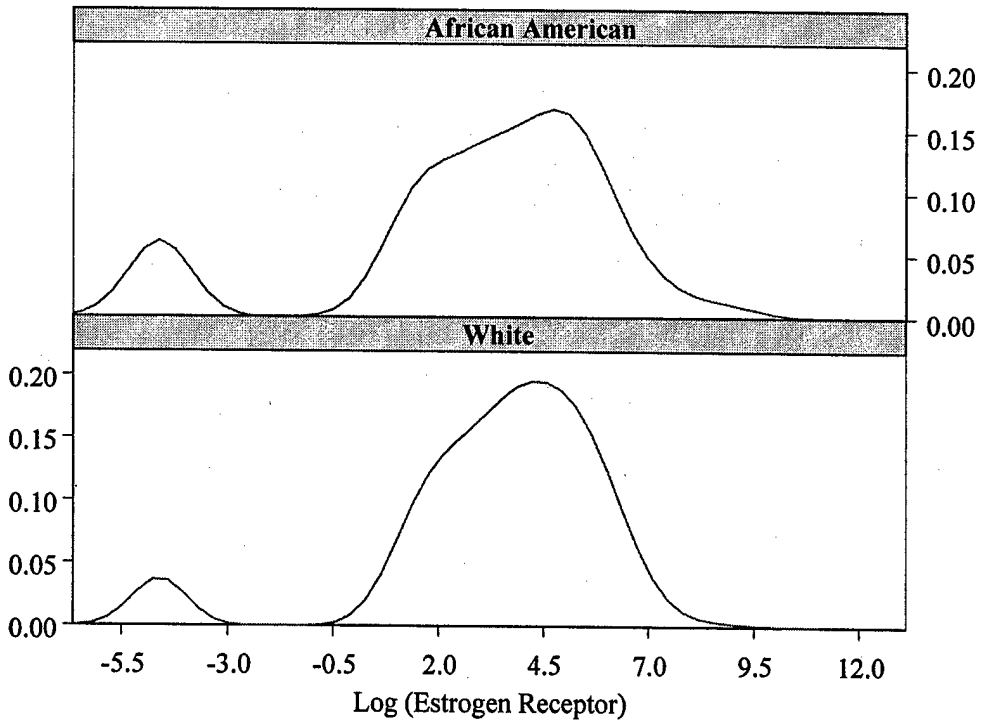


Figure 3. Distribution of study population by proportion in block groups living below the poverty level, stratified by race/ethnicity



ER data in the continuous scale was available for 614 individuals (1985-1989 inclusive). In 1990 the hormone receptor assays were switched to a histologic antibody assay, which were evaluated in the dichotomous scale. Thus, the 1990 hormone receptor data was not compatible with earlier data are not included in the analysis. Applying a receptor cutpoint of 10 femtomoles/mg, 350 of 444 Whites (78.8%) were ER positive and 124 of 170 (72.9%) Blacks were ER positive. PR data were available for 434 individuals: 100 of 118 (84.7%) Blacks were PR positive and 280 of 316 (88.6%) Whites were PR positive. The distribution of ER values is displayed graphically in Figure 4. African American patients had less ER positivity than their White counter parts (Table 1) ($OR_{Black\ vs.\ White}$ = 0.72, 95% CI 0.48, 1.09; p = 0.12) and this applied to both pre-menopausal ($OR_{Black\ vs.\ White}$ = 0.77, 95% CI 0.33, 1.76; p = 0.53) and post-menopausal women ($OR_{Black\ vs.\ White}$ = 0.62, 95% CI 0.38, 1.00; p = 0.05). Following adjustment for stage and age, the inverse association between African American race/ethnicity and ER positivity was even stronger: $OR_{Black\ vs.\ White}$ = 0.62 (95% CI 0.40, 0.97; p = 0.04).

Figure 4. Distribution of log(Estrogen Receptor in femtomoles/mg) values, by race/ethnicity



Survival Data

The median follow-up was 10.04 years (minimum 0.036, maximum 17.81 years). During the follow-up 483 deaths were observed in the 924 study subjects (52.3%).

Disparity in Survival – Univariate Analyses

The Kaplan Meier survival plot (Figure 5) and life table analysis (Table 2) demonstrate the significantly reduced survival observed in Black compared to White breast cancer patients in the HFHS study cohort. The hazard ratio (HR), Black versus White, was 1.34 (1.11, 1.62; p = 0.003).

Figure 5. Kaplan Meier survival plot describing the survival experience of Black and White breast cancer patients, HFHS 1985-1990 (p = 0.003)

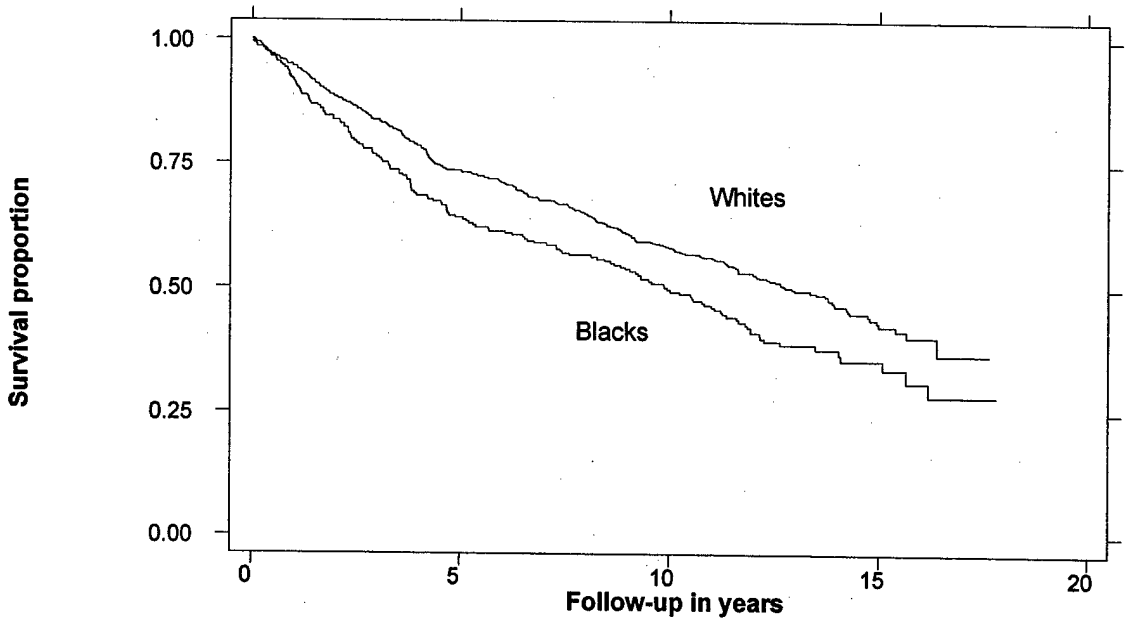


Table 2. Survival proportion at selected follow-up periods, by race/ethnicity

Years of follow-up	Black	White
0	1.0	1.0
3	76.2% (70.5-81.0)	83.7% (80.6-86.4)
5	64.1% (57.9-69.6)	73.5% (69.8-76.8)
10	49.6% (43.3-55.6)	58.2% (54.1-62.0)
15	34.8% (28.4-41.3)	43.6% (39.1-48.0)

KEY RESEARCH ACCOMPLISHMENTS

Study findings have contributed to scientific understanding of the following study questions.

Study Question 1. Does the continuous ER variable carry more predictive information than the dichotomous ER variable?

The hormone receptor data was right skewed. The skew test p-value testing the null hypothesis of normal distribution on untransformed ER data was < 0.001 and on log transformed data was 0.13. Statistical analysis was carried out on log transformed receptor data. Generally, because of limited tumor tissue sample sizes, and the priority being to carry out estrogen receptor analysis, more missing data existed for PR than for ER. Results presented here focus on analyses of ER data.

Adjusted for age and stage, the hazard ratios for logER as a continuous variable and ER dichotomized at 10 femtomoles/mg (ERdi10) were 0.93 (95% CI 0.87, 1.00; p = 0.05) and 0.69 (95% CI 0.53, 0.91; p = 0.007). The c statistic was used to estimate predictive value of each ER variable. In univariate Cox survival analysis, the c statistic for log ER and dichotomized ER were 50.25% and 52.82%, respectively. In addition to age and stage, log ER contributed no further to the c statistic whereas dichotomized ER contributed an additional 0.5% (c statistic 71.58% vs. 71.08%).

The relationship between ER and breast cancer recurrence/progression was evaluated by logistic regression analysis. Both ER variables were inversely associated with recurrence/ progression: OR_{logER} = 0.90 (95% CI 0.80, 1.01; p = 0.07; ROC AUC = 55.66%) and OR_{ERdi10} = 0.55 (95% CI 0.36, 0.83; p = 0.005; ROC AUC = 55.75%).

If ER data were more informative as a continuous rather than a dichotomous variable, it is expected that ER would demonstrate a dose-response relationship with outcomes. Such a graded relationship was assessed by evaluating log transformed ER data in four ordinal levels as indicated in Table 3, with the second (approximate), third and forth quartiles being compared to the lowest level (ER levels from 0 to 10 femtomoles/mg approximately represents the first quartile). For increasing levels compared to the baseline level, the adjusted hazard ratios for ER predicting survival were 0.69, 0.60, and 0.72 and adjusted odds ratios for ER predicting breast cancer recurrence/progression were 0.84, 0.59, and 0.63 (Table 3).

Thus, ER evaluated as a continuous variable was not a better predictor of survival and breast cancer recurrence/progression, than ER dichotomized at 10 femtomoles/mg. Indeed, the latter variable was slightly more predictive as judged by the c statistic and ROC AUC. In addition, absence of increasing protection with higher level positivity indicates that no dose-response

relationship exists and that all levels of positivity above 10 femtomoles/mg were similarly protective. These findings indicate that biologically ER receptor status appears to represent an "all-or-none" type of process and that 10 femtomoles/mg is a useful clinical cutpoint.

Table 3. Hazard ratios & odds ratios for three ordinal levels of log transformed estrogen receptor compared to the baseline level predicting survival & breast cancer recurrence/progression

ER indicator variable	Log-transformed ER values	Equivalent untransformed ER range	Hazard ratio * (95% CI; p-value) Outcome: Survival	Odds ratio † (95% CI; p-value) Outcome: Recurrence/progression
logERdv0	0‡ to 2.30	0 to 10 femtomoles/mg	baseline	baseline
logERdv1	>2.30 to 3.85 (50th percentile)	>10 to 47	0.69 (0.50, 0.95; p = 0.03)	0.84 (0.46, 1.52; p = 0.56)
logERdv2	>3.85 to 5.12 (75th percentile)	48 to 165	0.60 (0.42, 0.84; p = 0.003)	0.59 (0.31, 1.11; p = 0.10)
logERdv3	>5.12	166 to 10216	0.72 (0.52, 1.00; p = 0.05)	0.63 (0.34, 1.18; p = 0.15)

* Adjusted for age and stage
† Adjusted for stage
‡ 0.01 was added to values to avoid log transformation of zero, an impossible number.

<u>Study Question 2</u>. Does the inverse association between hormone receptor status and breast cancer outcomes (recurrence/progression & survival) differ between African American and White breast cancer patients?

In Cox survival regression analysis, adjusted for the important covariates, stage and age, the hazard ratio for estrogen receptor (dichotomized at 10 femtomoles/mg) was 0.71 (95% CI 0.46, 1.10; p = 0.13) for Black and 0.71 (95% CI 0.50, 1.00; p = 0.05) for White breast cancer patients. In logistic regression analysis, adjusted for stage, the odds ratio for association between ER dichotomized at 10 femtomoles/mg and breast cancer recurrence/progression was 0.59 (95% CI 0.25, 1.35; p = 0.21) for Black and 0.77 (95% CI 0.42, 1.40; p = 0.39) for White breast cancer patients. The magnitudes of effect estimates, overlapping confidence limits and absence of statistical interaction (not shown) suggest that the associations between estrogen receptor and the two aforementioned breast cancer outcomes does not differ substantially between Black and White breast cancer patients.

Study Question 3. What impact does comorbidity have on breast cancer outcomes and do differences in comorbidity explain race/ethnic disparities in breast cancer outcomes? Specifically,

3a. Does comorbidity explain receipt of breast cancer treatment, in particular, receipt of surgery, breast cancer recurrence/progression and survival?
3b. Do important, predictive comorbidities differ by race ethnicity?
3c. To what extent does comorbidity explain race/ethnic disparities in breast cancer outcomes?
3d. Which specific comorbidities are important in explaining the reduce survival experienced by African American breast cancer patients?

What comorbidities were studied? In this study, comorbidity data was collected for 259 more-or-less mutually exclusive diagnostic categories based on the *Clinical Classifications Software* (CCS) [47,48], which was developed by the Agency for Healthcare Research and Quality (U.S. Department of Health and Human Services) to facilitate health research by producing a manageable number of clinically meaningful disease categories from the >12,000 codes in the International Classification of Diseases, 9th Revision, Clinical Modifications [49]. This comorbidity list was further supplemented by comorbidity categories suggested to be important in our previous studies of comorbidity and lung cancer outcomes [20-22]. The comorbidity listings and their categories are provided in the Abstraction Form (AF) in Appendix 1. In summary, data on 268 comorbidities in 16 comorbidity categories were assessed (Table 4).

Table 4. Distribution of adverse comorbidities by ICD categories & subcategories

Comorbidity Category	ICD code	Number of subcategories	Adverse comorbidities ‡
1. Infectious & parasitic diseases	001-139	11	4
2. Neoplasia (prior to index breast cancer)	140-239	27	2*
3. Category 3 diseases = endocrine, nutritional, metabolic & immune diseases	240-279	35	3
4. Blood & blood-forming organs	280-289	6	1†
5. Mental disorders	290-319	11	4
6. Nervous system & sensor organs	320-389	21	10
7. Circulatory system	390-459	26	19
8. Respiratory system	460-519	17	7
9. Digestive system	520-579	21	10
10. Genitourinary system	580-629	21	3
11. Complications of pregnancy, childbirth & puerperium	630-679	21	‡
12. Skin & subcutaneous tissue	680-709	4	‡
13. Musculoskeletal system & connective tissue	710-739	14	6
14. Congenital anomalies	740-759	5	‡
15. Conditions of perinatal period	760-779	7	‡
16. Injury, trauma & poisoning	800-999	21	6
	Total	268	75

Abbreviations: ICD, international classification of disease.
* Pooled into cancer & metastatic cancer
† For blood anemia and other blood diseases were pooled
‡ Although data for these comorbidity categories were collected, they were excluded from analysis because they *a priori* and/or statistically were not associated with breast cancer outcomes.

Adverse comorbidities were defined as those comorbidities that had significantly elevated Cox regression hazard ratios regardless of effect magnitudes, that had hazard ratios >1.20 regardless of statistical significance or that were deemed to be adverse *a priori* based on clinical knowledge and/or past research. Examples of the latter include HIV/AIDS and asthma. The specific adverse comorbidities in their comorbidity categories are presented in Table 5.

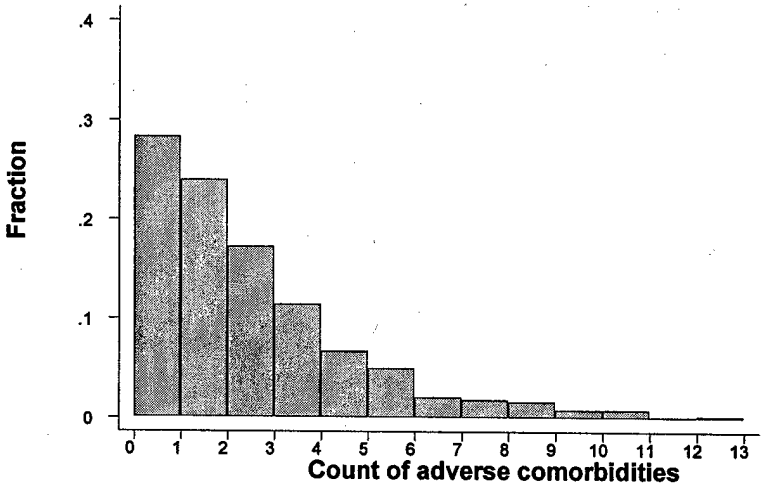
Table 5. Specific adverse comorbidities in comorbidity categories

Comorbidity Category	Specific adverse comorbidities
1. Infectious & parasitic diseases	tuberculosis, septicemia, HIV/AIDS, viral infection
2. Neoplasia	any cancer other than non-melanotic skin cancers, metastatic cancer
3. Category 3 (endocrine, nutritional, metabolic & immune)	diabetes without complications, diabetes with complications, nutritional deficit – under nutrition, & fluid/electrolyte/mineral imbalance
4. Blood & blood-forming organs	anemia, blood disease other than primary anemia
5. Mental disorders	alcohol abuse, substance abuse, senility/dementia, & history of mental health disease/problem monitoring
6. Nervous system & sensor organs	meningitis, other central nervous system (CNS) infections (AF cm78), Parkinson's disease, other CNS disorders (AF cm81), paralysis, epilepsy, retinal disease, glaucoma, blindness, and other nervous system disorders (AF cm95)
7. Circulatory system	carditis/myopathy, hypertension, infarction, coronary heart disease, angina, pulmonary cardiac disease (cor pulmonale), other heart disease (AF cm104), conduction disorders, arrhythmia, congestive heart failure, acute cerebrovascular disease, pre-cerebral artery occlusion/stenosis, other cerebrovascular diseases (AF cm111), transient cerebral ischemia, plegia, peripheral visceral atherosclerosis, aneurysms, arterial embolism/thrombosis, & other circulatory disease (AF cm116)
8. Respiratory system	emphysema, asthma, pulmonary fibrosis, aspiration pneumonia, pleurisy/atelectasis, respiratory failure, pneumoconioses
9. Digestive system	ulcer, gastritis, other gastroduodenal diseases (AF cm 141), abdominal hernia with complications, intestinal obstruction, anorectal disease, biliary tract disease, alcohol-related liver disease, pancreatic disease, gastrointestinal bleeding
10. Genitourinary system	acute renal failure, chronic renal failure, other lower urinary tract diseases (AF cm162)
13. Musculoskeletal system & connective tissue	osteoporosis/osteoparesis, pathologic fracture, other acquired deformities (AF cm209), systemic lupus erythematosus, limb amputation, hip replacement
16. Injury, trauma & poisoning	hip fracture, other fracture (AF cm231), open head wound, open wound to extremities, burns, non-medical poisoning

Abbreviations: AF, abstraction form (Appendix 1).

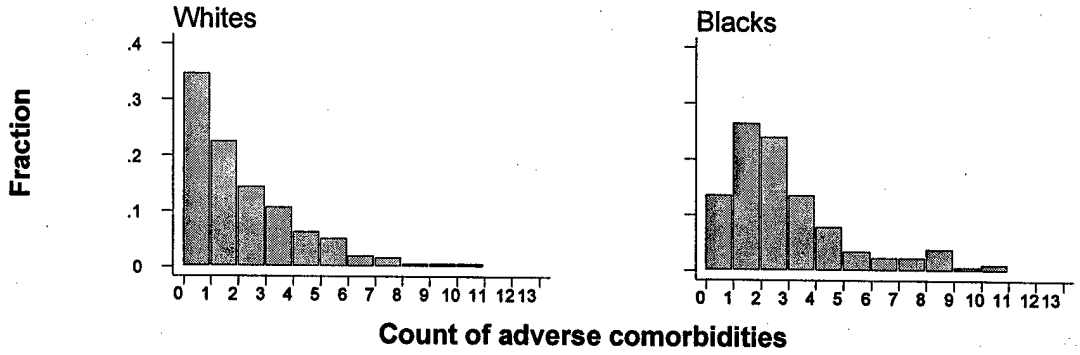
Distribution of adverse comorbidity. Comorbidity data was complete for 94.9 percent of subjects. For those with comorbidity data, 28.3% had no adverse comorbidities. For adverse comorbidity, the mean, median, and range were 2.02, 1, and 0-13. The distribution of adverse comorbidities is presented in Figure 6.

Figure 6. Distribution of the number of comorbidities per individual



Association between race/ethnicity and adverse comorbidity. The mean, median and range of adverse comorbidities for Blacks was 2.45, 2, 0-10 and for Whites was 1.83, 1, 0-13 (t-test comparing means p = 0.0001). The distributions of adverse comorbidities by race/ethnicity are presented in Figure 7. Of Blacks 85.9 percent and of Whites 65.7 percent had one or more adverse comorbidities (p < 0.001). The odds ratio, Black versus White, for having adverse comorbidity (≥1 vs. 0) was 3.19 (95% CI 2.16, 4.71; p < 0.001).

Figure 7. Distribution of the number of comorbidities per individual stratified by race/ethnicity



Comorbidity & Surgery. For patients with stage I-IV breast cancer, the most protective treatment intervention was surgery, which was similarly protective in early stage (I & II) and advanced stage (III & IV) disease: $HR_{yes\ vs.\ no}$ = 0.37 (95% CI 0.21, 0.64; p < 0.001) and $HR_{yes\ vs.\ no}$ = 0.38 (95% CI 0.24, 0.62; p < 0.001), respectively.

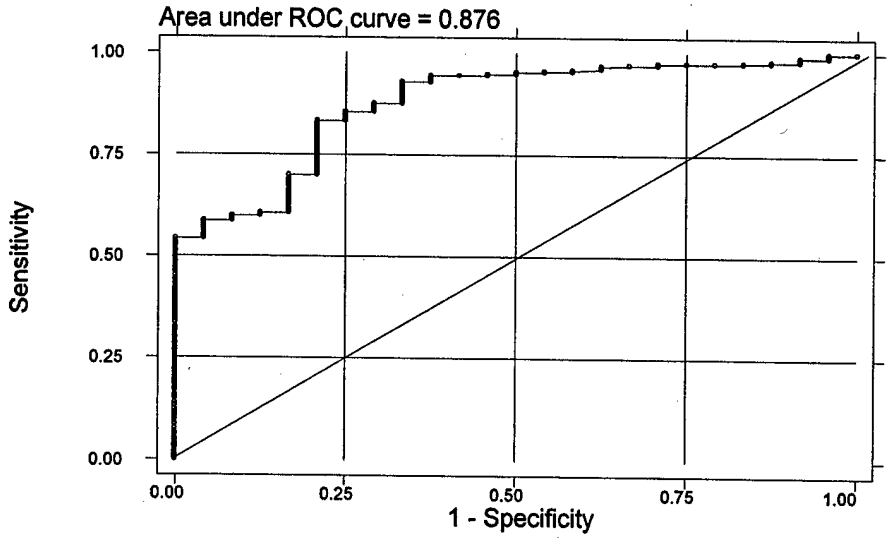
The relationship between receipt of surgery and adverse comorbidity (AC) was assessed using logistic regression with adverse comorbidity evaluated in five roughly comparable sized groups of 0, 1, 2, 3 and 4-13 adverse comorbidities. The univariate odds ratio for surgery per one level of adverse comorbidity quintile group was 0.71 (95% CI 0.57, 0.88; p = 0.001). Adjusted for age, marital status, SES (block group poverty level) and stage, the odds ratio per one level of adverse comorbidity quintile was 0.74 (95% CI 0.52, 1.05; p = 0.09). Adjusted for the aforementioned covariates, compared to the baseline of 0 adverse comorbidities, the odds ratio for receipt of surgery was 0.78 for those with 1 adverse comorbidity, 0.70 for those with 2 adverse comorbidities and 0.26 for those with ≥4 adverse comorbidities (the estimate for those with 3 adverse comorbidities was undefined). These observations indicate that adverse comorbidities are associated with non-receipt of surgery in a dose-response fashion and that not all of the effect is explained away by other predictors.

In multivariate analysis, the magnitude of effect estimate suggests that the following specific categories of comorbidities are associated with reduced likelihood of receipt of surgery (Table 6): previous metastatic cancer, mental disorders, cardiovascular disease, respiratory disease, digestive tract disease and history of injury/trauma/poisoning (Table 6). In particular, respiratory disease was significantly associated with reduced likelihood of surgery. The model presented in Table 6 has a pseudo-R^2 of 0.246 and a ROC AUC of 0.876 (Figure 8), indicating that it explains data variation and is predictive of the outcome. The comparable model excluding comorbidities has a pseudo-R^2 of 0.206 and a receiver operator characteristic area under the curve of 0.823.

Table 6. Multivariate logistic regression model predicting receipt of surgery in breast cancer patients, HFHS 1985-1990

Predictor variables	Odds ratio (95% confidence intervals; p-value)
Age per 10 years	0.55 (0.35, 0.86; p = 0.009)
Stage (in 4 AJCC levels)	0.32 (0.20, 0.50; p < 0.001)
Comorbidity categories	
Previous metastatic cancer (yes vs. no)	0.30 (0.04, 2.49; p = 0.26)
Mental disorders (per one)	0.74 (0.21, 2.58; p = 0.64)
Cardiac disorders (per one)	0.89 (0.63, 1.21; p = 0.43)
Respiratory disorders (per one)	0.21 (0.05, 0.86; p = 0.03)
Digestive tract disorders (per one)	0.73 (0.37, 1.43; p = 0.36)
History of injury/trauma/poisoning (per one)	0.57 (0.11, 2.83; p = 0.49)

Figure 8. The Receiver Operator Characteristic Curve for the logistic model presented in Table 6



Blacks received modestly less surgery than Whites (93.9 vs. 95.6%; $OR_{Black\ vs.\ White}$ = 0.71, 95% CI 0.37, 1.37; p = 0.31). However, all of this difference was explained by stage (stage adjusted $OR_{Black\ vs.\ White}$ = 1.12, 95% CI 0.54, 2.36; p = 0.76). In conclusion, adverse comorbidity was associated with non-receipt of treatment, but race/ethnic differences in receipt of surgery were modest and were not explained by comorbidity.

Comorbidity & Breast Cancer Progression / Recurrence

Associations between comorbidities and cancer progression/recurrence have not been well studied, and we are unaware of compelling biologic reasons to suspect direct relationships. However, comorbidity can lead to inferior treatment and thus has the potential to indirectly lead to cancer progression/recurrence. Logistic regression analysis was used to study the associations between *breast cancer progression/recurrence* and predictor variables (Table 7). *Adverse comorbidities*, collectively or comorbidity classes individually, demonstrated no strong or important associations with progression/recurrence.

Table 7. Logistic regression odds ratios (95% CI; p-value) describing the association between breast cancer progression/recurrence and selected predictors

Predictor variable	Univariate	Multivariate
Race/ethnicity (Black vs. White)	1.47 (1.06, 2.03; p = 0.02)	1.29 (0.85, 1.95; p = 0.23)
ER (≥10 vs. <10 femtomole/mg)	0.55 (0.36, 0.83; p = 0.005	0.77 (0.45, 1.30; p = 0.33)
Stage (IV, III, II , I as ordinal)	3.91 (3.05, 5.01; p < 0.001)	3.58 (2.73, 4.69; p < 0.001)
Socioeconomic status (BGPBPL)	9.25 (1.43, 59.75; p = 0.02)	dropped from model
Surgery (yes vs. no)	0.14 (0.07, 0.29; p < 0.001)	0.16 (0.06, 0.48; p = 0.001)
Chemotherapy (yes vs. no)	2.54 (1.82, 3.53; p < 0.001)	1.55 (1.02, 2.36; p = 0.04)
Radiation therapy (yes vs. no)	1.82 (1.31, 2.52; p < 0.001)	1.76 (1.18, 2.64; p = 0.006)

Abbreviations: BGPBPL, block group proportion below poverty.

Comorbidity & Breast Cancer Survival

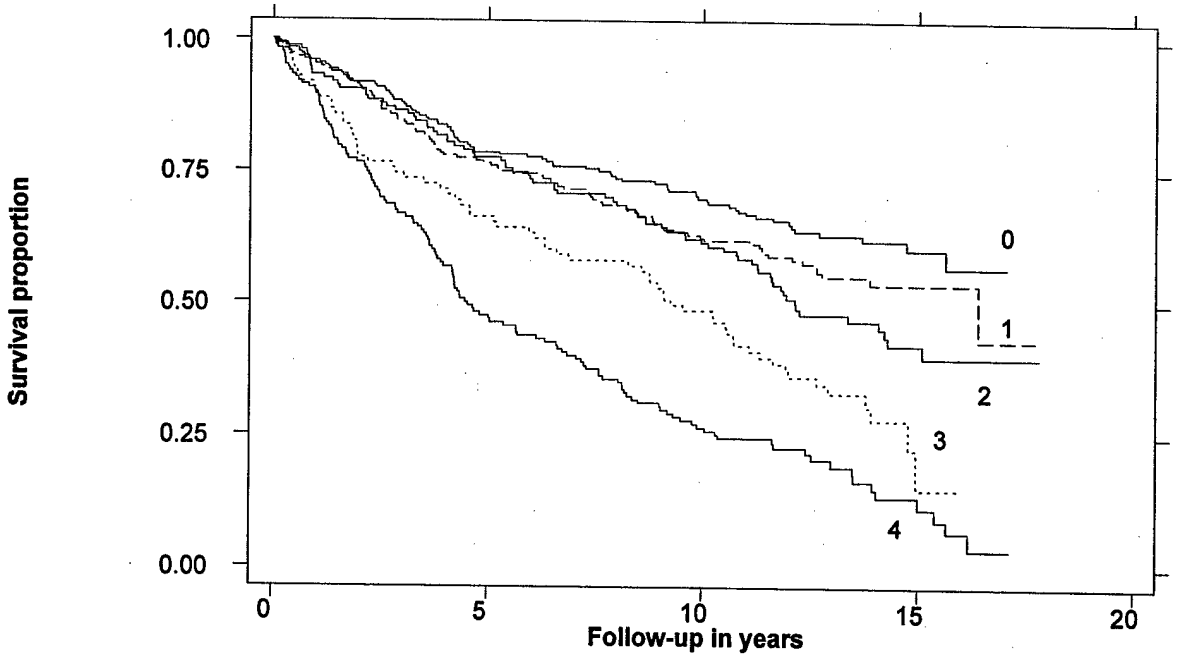
The univariate hazard ratio for adverse comorbidity as a single five-level variable (0, 1, 2, 3, & 4-13) was 1.40 (95% CI 1.31, 1.49; $p < 0.001$). Following adjustment for age, stage and ER positivity, surgery, chemotherapy, and radiation therapy, the hazard ratio for 5-level adverse comorbidity was 1.30 (95% CI 1.18, 1.44; $p < 0.001$). The dose-response relationship between adverse comorbidities and decreased survival was study with indicator variables corresponding to five levels of adverse comorbidity (Table 8). The unadjusted and multivariate models confirm that the hazard associated with adverse comorbidity increases with their quantity (Table 8). The survival plot stratified by the five adverse comorbidity levels is presented in Figure 9.

Table 8. Univariate and multivariate Cox regression hazard ratios (95% confidence intervals; p-value) for five levels of adverse comorbidity

	Unadjusted model	Multivariate model*
0 Adverse comorbidities	baseline	baseline
1 vs. 0 Adverse comorbidities	1.25 (0.93, 1.69; p = 0.13)	1.04 (0.70, 1.55; p = 0.86)
2 vs. 0 Adverse comorbidities	1.51 (1.11, 2.05; p = 0.009)	1.17 (0.77, 1.78; p = 0.46)
3 vs. 0 Adverse comorbidities	2.37 (1.72, 3.27; p < 0.001)	1.54 (0.98, 2.44; p = 0.06)
4-13 vs. 0 Adverse comorbidities	3.74 (2.85, 4.92; p < 0.001)	2.73 (1.79, 4.15; p < 0.001)

* Multivariate model is adjusted for age, stage, ER positivity, surgery, chemotherapy and radiation therapy.

Figure 9. Kaplan Meier survival plot of breast cancer patients stratified by five strata of adverse comorbidities (0, 1, 2, 3, 4-13), HFHS 1985-1990



As was previously described, Black patients had significantly more adverse comorbidities than White patients, and adverse comorbidities are a powerful predictor of reduced survival. Adverse comorbidity explains 35.3 percent of African American disparity in survival: unadjusted $HR_{Black\ vs.\ White}$ = 1.340 (95% CI 1.11, 1.62; p = 0.003) and the adverse comorbidity-adjusted $HR_{Black\ vs.\ White}$ = 1.220 (95% CI 1.00, 1.48; p = 0.05). Adverse comorbidity was most important in explaining race/ethnic survival disparity in individuals <70 years of age: Compared to the univariate hazard ratio (Black vs. White), the comorbidity-adjusted $HR_{B\ vs.\ W}$ declined substantially from 1.228 to 1.070 (a decline of 69.5%) (Table 9). In the older age group there was minimal change. One or more adverse comorbidities was present in 78.7% of Blacks and 56.9% of Whites (p < 0.001) in the <70 years group and in 97.0% of Blacks and 89.0% of Whites in the ≥70 year group (p = 0.02). This is an important observation because it indicates that overcoming the adverse effects of comorbidity in African Americans breast cancer patients <70 years has the potential to lead to long term benefits. It is also noteworthy that the complete model in Table 9 explains all of the race/ethnic disparity in patients <70 years, but a substantial amount of disparity remains unexplained in the ≥70 years group. Of particular importance in explaining race/ethnic disparities in survival were cardiovascular disease as a group, and hypertension, heart disease, cerebrovascular disease, and diabetes, specifically (data not shown).

Table 9. Univariate and multivariate hazard ratios (95% CI; p-value) for race/ethnicity and covariates, stratified by age, dichotomized at ≥70 years

Predictor variable	Univariate; Age <70 years	Univariate; Age ≥70 years
Race/ethnicity (Black vs. White)	1.23 (0.94, 1.61; p = 0.14)	1.26 (0.95, 1.66; p = 0.11)
	Multivariate; Age <70 years	**Multivariate; Age ≥70 years**
Race/ethnicity (Black vs. White)	1.07 (0.81, 1.42; p = 0.64)	1.26 (0.95, 1.67; p = 0.11)
Adverse comorbidity (5 levels)	1.35 (1.23, 1.48; p < 0.001)	1.26 (1.13, 1.40; p < 0.001)
	Multivariate; Age <70 years	**Multivariate; Age ≥70 years**
Race/ethnicity (Black vs. White)	0.95 (0.68, 1.34; p = 0.77)	1.18 (0.83, 1.68; p = 0.34)
Adverse comorbidity (5 levels)	1.18 (1.05, 1.32; p = 0.006)	1.14 (1.01, 1.30; p = 0.04)
Age (per 10 years)	1.12 (0.96, 1.30; p = 0.14)	1.82 (1.36, 2.44; p < 0.001)
Stage (4 AJCC levels)	2.29 (1.92, 2.72; p < 0.001)	1.62 (1.35, 1.95; p < 0.001)
Adverse symptoms (4 levels)	1.39 (1.17, 1.64; p < 0.001)	1.01 (0.83, 1.23; p = 0.90)
SES (% <grade 12)	1.01 (1.00, 1.02; p = 0.03)	1.01 (0.99, 1.02; p = 0.38)
Surgery (yes vs. no)	0.91 (0.50, 1.64; p = 0.75)	0.44 (0.25, 0.77; p = 0.004)

Study Question 4. Do the comprehensive comorbidity data collected in the current study suggest deficiencies in evaluating breast cancer survival and disparities using established measures of comorbidity, such as the Charlson Comorbidity Index?

The c statistic for univariate Cox regression models including adverse comorbidity count as a single variable was 62.4% and for the Charlson Comorbidity Index was 58.5%. These c statistics indicate that the simple unweighted count of adverse comorbidities predicts survival better than the Charlson Comorbidity Index does. Furthermore, the unadjusted hazard ratio for race/ethnicity (Black vs. White) was 1.340 (95% CI 1.11, 1.62; p = 0.003), the adverse comorbidity count-adjusted $HR_{Black\ vs.\ White}$ was 1.220 (95% CI 1.00, 1.48; p = 0.05), and the Charlson Index-adjusted $HR_{Black\ vs.\ White}$ was 1.256 (95% CI 1.03, 1.53; p = 0.02). Thus, adverse comorbidity count explained 35.3% of race/ethnic disparity in survival and the Charlson explained only 24.7% of the disparity. These findings indicate that the Charlson is not an optimal method of comorbidity measurement for studies of breast cancer survival and disparities. We are carrying out further comparisons with additional comorbidity measures and characterizing and quantifying important differences. This work will be reported when complete.

Study Question 5. To what extend do presenting symptoms predict reduced survival? Are prognostic adverse symptoms associated with race/ethnicity and do they explain disparities in breast cancer outcomes?

Whereas cancer stage is a measure of morphologic extent of disease, cancer-associated presenting symptoms are a pathophysiologic gauge of extent of cancer, and may carry important prognostic information independently of stage. We found that adverse symptoms were important independent predictors of lung cancer outcomes and disparities [23]. In this study, symptoms data was collected for 36 symptoms in 7 categories (Appendix 1). Selection of symptoms came from the *Clinical Classification Software* [47,48] and from our previous research [23].

Presenting ***adverse symptoms*** (pretreatment) were those that had significantly elevated hazard ratios or had clinically meaningfully elevated hazard ratios regardless of significance (all had hazard ratios ≥1.5). Sixteen of 36 symptoms were adverse: syncope, fatigue, fever, weight loss, nausea/vomiting, anorexia, jaundice, dyspnea, hemoptysis, lymphadenitis, lymphadenopathy, headache, ocular symptoms, insomnia, neurological symptoms, and alopecia.

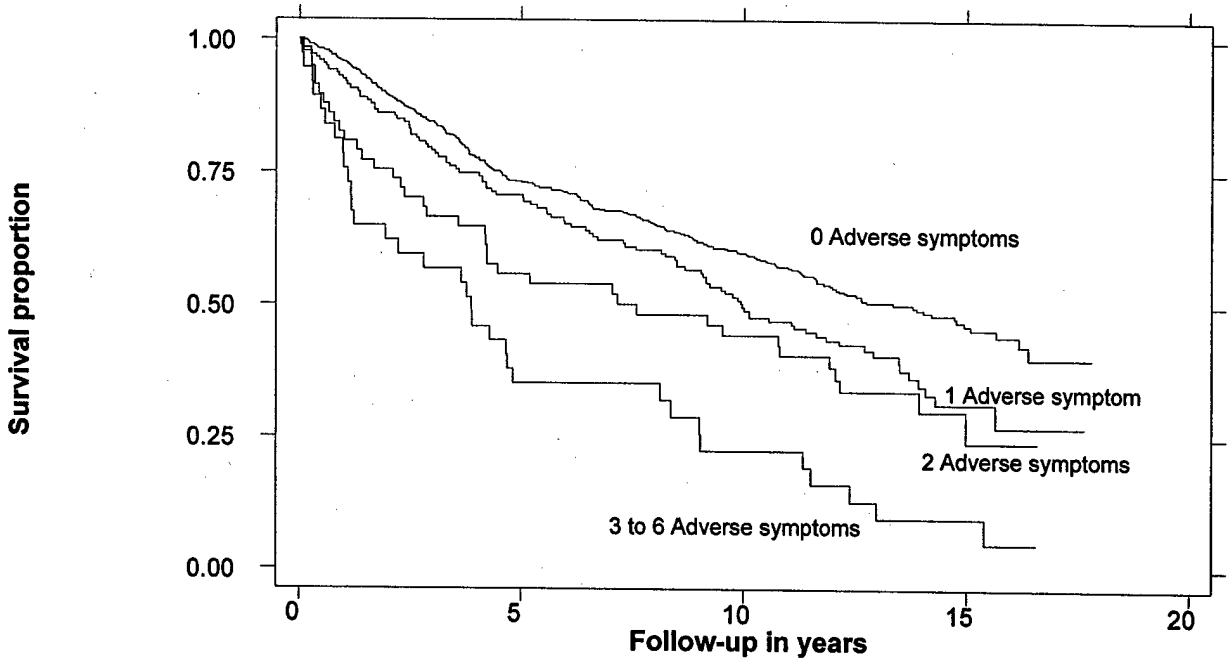
Table 10. Adverse presenting symptoms (pre-treatment): hazard ratio, and distributions and associations with race/ethnicity

	Hazard Ratio (95% CI; p-value)	Black	White	p-value exact	Odds Ratios (B vs. W) (95% CI; p-value)
Syncope	1.68 (1.04, 2.73; p = 0.04)	3.21	3.02	0.83	1.07 (0.46, 2.48; p = 0.88)
Fatigue	1.36 (1.00, 1.85; p = 0.05)	9.24	8.56	0.79	1.09 (0.65, 1.82; p = 0.75)
Fever	1.55 (0.83, 2.91; p = 0.17)	1.20	2.01	0.57	0.59 (0.17, 2.12; p = 0.42)
Weight loss	2.23 (1.58, 3.13; p < 0.001)	5.62	5.03	0.73	1.12 (0.59, 2.16; p = 0.73)
Nausea/vomiting	1.50 (1.04, 2.16; p = 0.03)	6.43	4.70	0.31	1.39 (0.74, 2.62; p = 0.31)
Anorexia	3.33 (1.98, 5.57; p < 0.001)	3.21	1.34	0.09	2.44 (0.91, 6.58; p = 0.08)
Jaundice	20.55 (6.44, 65.63; p < 0.001)	0.80	0.17	0.21	4.82 (0.43, 53.38; p = 0.20)
Dyspnea	1.58 (1.23, 2.02; p < 0.001	0.40	1.17	0.45	0.34 (0.04, 2.77; p = 0.31)
Hemoptysis	3.18 (0.79, 12.75; p = 0.10)	0.00	0.34	1.00	NA
Lymphadenitis	1.91 (0.90, 4.03; p = 0.09)	1.61	1.17	0.74	1.37 (0.40, 4.74; p = 0.61)
Lymphadenopathy	1.74 (1.18, 2.55; p = 0.005)	5.62	4.87	0.73	1.16 (0.69, 2.24; p = 0.65)
Headache	1.78 (0.57, 5.55; p = 0.32)	0.40	0.34	1.00	1.20 (0.11, 13.27; p = 0.88)
Ocular symptoms	1.58 (0.94, 2.64; p = 0.08)	2.01	2.35	1.00	0.85 (0.30, 2.39; p = 0.76
Insomnia	1.54 (0.82, 2.88; p = 0.18)	1.61	1.51	1.00	1.06 (0.32, 3.49; p = 0.92)
Neurologic symptoms	40.93 (5.49, 304.96; p < 0.001)	0.00	0.17	1.00	NA
Alopecia	4.00 (1.28, 12.52; p = 0.02)	0.00	0.50	0.56	NA
Adverse symptoms (≥1 vs. 0)	1.61 (1.33, 1.95; p < 0.001)	36.55	30.87	0.13	1.29 (0.94, 1.76; p = 0.11)

Adverse Symptoms & Survival

The univariate hazard ratio for adverse symptom count was 1.34 (per one adverse symptom) (95% CI 1.23, 1.46; $p < 0.001$) and the c statistic for this variable alone was 56.1%. The dose-response association between adverse symptoms and decreased survival is depicted in Figure 10, with adverse symptoms stratified into four levels (0, 1, 2, & 3-6). Adjusted for age, stage, ER, adverse comorbidities, and surgery, the HR per 1 adverse symptom was 1.16 (95% CI 1.03, 1.32; $p = 0.02$).

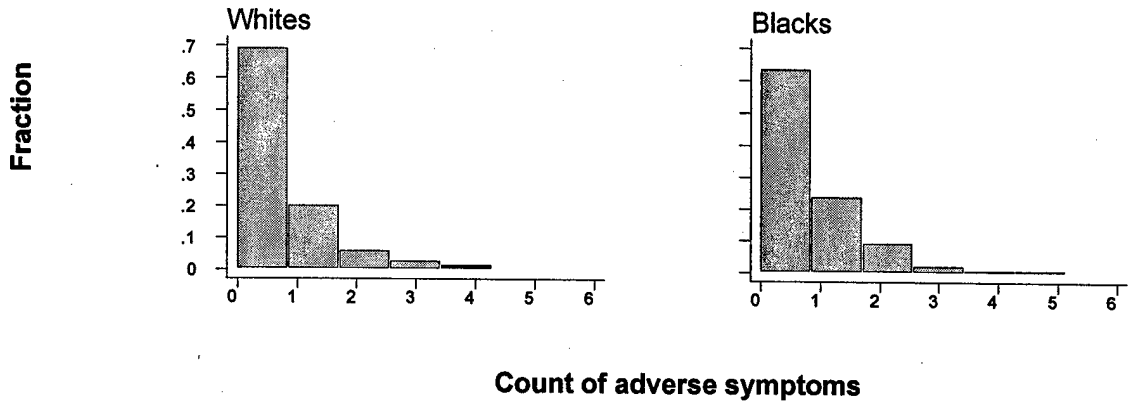
Figure 10. Kaplan Meier plot of the survival experience of breast cancer patients stratified by number of adverse symptoms



Adverse Symptoms & Race/ethnicity

Of Black patients 36.5 percent and of White patients 30.9 percent had ≥1 adverse symptom ($OR_{Black\ vs.\ White}$ = 1.29, 95% CI 0.94, 1.76; p = 0.11) (Figure 11). However, the unadjusted and adverse symptoms-adjusted hazard ratios for race/ethnicity were the similar and thus adverse symptoms evaluated by adverse symptoms count did not explain disparity to any important extent.

Figure 11. Distribution of adverse symptoms by race/ethnicity



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REPORTABLE OUTCOMES

The reportable outcomes (study findings) have been detailed in the *BODY* section. They are summarized here.

1. Breast cancer estrogen receptor status measured in the continuous scale does not carry more predictive information than ER status dichotomized at 10 femtomoles/mg in predicting breast cancer progression/recurrence and survival.
2. The association between ER status and breast cancer progression/recurrence and survival does not differ significantly between African American and White breast cancer patients.
3. Comorbidity is an important determinant of breast cancer survival. Adverse comorbidities occur significantly more in Black compared to White breast cancer patients and explains important amounts of race/ethnic disparity in survival.
4. Methodologic issues exist regarding the measurement of comorbidity for the purposes of predicting breast cancer outcomes. The popular Charlson Comorbidity Index, which has been "validated" in breast cancer patients, fails to capture a substantial amount of information predicting survival and explaining disparities compared to the more exhaustive detailed comorbidity inventory used in the current study.
5. Adverse breast cancer presenting symptoms were an important predictor of reduced survival, independent of stage and other prognostic factors: adjusted for stage, age, and ER status, the hazard ratio for adverse symptoms ($\geq$1 vs. 0) was 1.43 (95% CI 1.18, 1.75; $p < 0.001$). Although Black patients tended to have more adverse symptoms than Whites, adverse symptoms explained minimal amounts of disparity in survival.

Study findings 3, 4 and 5 are in addition to the original Statement of Work, that is, findings, 1 and 2. Four manuscripts are being prepared to describe study findings for 1 & 2, 3, 4, and 5 above. Upon completion they will be sent to the Department of Defense. An earlier abstract was presented at the Era of Hope in 2002 and an updated abstract describing selected study findings has been submitted for presentation at the *2005 Era of Hope* (Appendix 2).

Work carried out in this grant laid some of the foundation which led to the recent awarding of the following grant to Dr. Tammemagi, Principal Investigator:
Comorbidity & Symptoms and African American Disparities in Cancer Outcomes. Pilot study in the NCI Cancer Research Network (Wagner), NCI U19 CA 079689. (March 2004).
In turn, an NIH R01 grant, *Comorbidity & Symptoms and African American Disparities in Cancer Outcomes*, was submitted by Dr. Tammemagi in October 2004.

CONCLUSIONS

This Department of Defense-funded study found that estrogen receptor positivity was associated with breast cancer recurrence/progression and survival in an "all-or-none" fashion rather than a dose-response fashion, and did so similarly in Blacks and Whites. Although these findings do not enable us to use hormone receptor data to identify patients at particularly higher or lower risk of worse survival, it does add to our understanding of breast carcinogenesis and does justify continued use of current dichotomous interpretations of hormone receptor assays.

In addition, this study demonstrated that adverse comorbidities were important independent predictors of reduced survival, occurred more frequently in Black patients and explained important amounts of race/ethnic disparity in survival. The importance of comorbidity measurement methodology in studying breast cancer outcomes and disparity was revealed. The study found that presenting adverse symptoms are an important independent predictor of survival. This knowledge can be used to identify susceptible patients requiring increased monitoring, more aggressive treatment and management of comorbidities. This is expected to lead to improved survival in general and the reduction of disparity. To be effectively implemented, future work needs to identify the specific characteristics of individual comorbidities that are associated with adverse outcomes. We are striving to work in this direction. In addition, the root causes of adverse comorbidities, especially in African American need to be identified so that primary preventative measures can be instituted.

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APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

Study ID #: _____
Abstraction Date: __/__/_____ **Abstraction Time:** _____
Abstractor ID: _____ (use month/day/ year throughout)

CASE DESCRIPTION & EPIDEMIOLOGIC DATA

CONFIRMATION OF CASE STATUS

Is there evidence in the chart that the patient was diagnosed with breast cancer or suspicion of invasive breast cancer on the same date (or within 2 weeks of the date) as it appears as the "Diagnosis Date" for the Josephine Ford Cancer Registry?

If Yes☒ Continue.
Record original JFCC dx date here: __/__/_____

If No ☒ Do alternative breast cancer diagnosis dates exist?
Please enter the dates here:

1. __/__/_____
2. __/__/_____
3. __/__/_____

If you are unable to confirm diagnosis of invasive breast cancer, **STOP REVIEW** and consult with investigator.

SOCIODEMOGRAPHIC DATA (Complete only if it differs from that provided, i.e., JFCC Tumor Registry data)

Name Last:_____ **First:** _____ **Middle Initial:** ____

Address at diagnosis: Street Address _____

City _____ State _____ ZIP Code _____

Current address, if different from diagnosis address

Street Address _____

City _____ State _____ ZIP Code _____

Date of Birth: ____/____/_____

Race
1 = White
2 = Black / African American
3 = American Indian or Alaskan Native
4 = Asian
5 = Pacific Islander or Native Hawaiian
6= Other, specify_____
9 = Unknown

Ethnicity 0= Non-Hispanic 1 = Hispanic

Marital Status at diagnosis
1= Married or living as married
2 = Not married 2a = Single (never married)
2b = Divorced or legally separated
2c = Widowed
9= Unknown

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

BODY SIZE INFORMATION (exclude data during pregnancy)

Maximum Height (inches): _____ Date: __ __ / __ __ / __ __ __ __

Pre-diagnosis weight closest to **diagnosis date** (pounds): _____ Date: __ __ / __ __ / __ __ __ __

REPRODUCTIVE / ENDOCRINE HISTORY (Mark NA if data are not available)

Age at menarche (years) _____

Menopausal status at diagnosis.
01= Pre-menopausal
02= Peri-menopausal (Transition between pre- & post-menopause. Menstrual cycles irregular, hot flashes.)
03= Post-menopausal When did menopause occur? _____Year/age/years ago?
04= Hysterectomy. Number of ovaries removed? _____ Date of surgery: __ __/__ __/__ __ __
99=Undetermined

Parity (# of live births) as of the diagnosis date. __ __

If pre-menopausal, record the number of post-diagnosis live births __ __

Did the patient use <u>hormone contraceptives</u>? 0=No 1=Yes 9=Unknown

Start date of use: __ __ / __ __ / __ __ __ __ Type : 1=Birth Control Pills
Length of time (years): _____ 2=Shots or Injections
Product Name: _____ 3=Subdermal Implants

Start date of use: __ __ / __ __ / __ __ __ __ Type: 1=Birth Control Pills
Length of time (years): _____ 2=Shots or Injections
Product Name: _____ 3=Subdermal Implants

Start date of use: __ __ / __ __ / __ __ __ __ Type: 1=Birth Control Pills
Length of time (years): _____ 2=Shots or Injections
Product Name: _____ 3=Subdermal Implants

Did the patient use <u>hormone replacement therapy</u>? 0=No 1=Yes 9=Unknown

Start date of use: __ __ / __ __ / __ __ __ __ 1=Estrogen Alone
Length of time (years): _____ 2=Estrogen plus Progesterone
Product Name: _____ 3=Progesterone Alone
4=Other

Start date of use: __ __ / __ __ / __ __ __ __ 1=Estrogen Alone
Length of time (years): _____ 2=Estrogen plus Progesterone
Product Name: _____ 3=Progesterone Alone
4=Other

Start date of use: __ __ / __ __ / __ __ __ __ 1=Estrogen Alone
Length of time (years): _____ 2=Estrogen plus Progesterone
Product Name: _____ 3=Progesterone Alone
4=Other

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

FAMILY HISTORY OF BREAST CANCER

Is there a family history of breast cancer? (BRCA)

1= Yes, there is a noted family history
2= No, there is a noted negative family history of BRCA
8 = record shows "Ø"
9=Undetermined, not documented

MAMMOGRAPHY HISTORY

Mammography History from 3 years prior to first treatment: 0=No 1=Yes 9=Unknown

If yes, complete the following table

	Dates:	Results: Left	Results: Right
1.	__/__/____		
2.	__/__/____		
3.	__/__/____		
4.	__/__/____		
5.	__/__/____		
6.	__/__/____		
7.	__/__/____		
8.	__/__/____		
9.	__/__/____		
10.	__/__/____		
11.	__/__/____		
12.	__/__/____		
13.	__/__/____		
14.	__/__/____		
15.	__/__/____		

Results Key

1= Negative
2= Benign/Negative
3= Probably Benign
4= Suspicious
5= Highly Suspicious
8= Incomplete/Inconclusive
9= Unknown

PATIENT HISTORY OF BREAST LESIONS *BEFORE* THE INDEX BREAST CANCER

Breast Biopsy History throughout patient records

0=No 9=Unknown

1=Yes If yes, complete table below

Dates	**Results** (specify L/R)
__/__/____	
__/__/____	
__/__/____	
__/__/____	
__/__/____	
__/__/____	
__/__/____	
__/__/____	
__/__/____	

Key to Results:

1. Benign Breast Disease (BBD)
2. Ductal Carcinoma In Situ (DCIS)
3. Lobular Carcinoma In Situ (LCIS)
4. Both BBD and CIS/Cancer
5. Invasive Carcinoma (specify histopathologic type)
6. Lumpectomy or Mastectomy (unilateral or bilateral) not further specified
7. Cosmetic Breast Reduction
8. Cosmetic Breast Enlargement
9. Other Breast Biopsy (epithelial biopsy of breast skin, nipple, fat, axillary lymph nodes, etc.)
99. Incomplete/Inconclusive Unknown

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

SYMPTOMS AND LEAD-UP TO THE DIAGNOSIS OF BREAST CANCER

When was the first time that a suspicion of breast cancer for this index case of breast cancer was documented in medical records or indicated by a medical procedure? __ __ / __ __ / __ __ __ __

Did patient report breast symptoms? ☒ 01=Yes ☒ If yes, please continue with the next question.

☒ 02=No. Explicit mention of no symptoms☒ If no, skip to next box.

☒ 99=No comment about symptoms ☒ Skip to next box.

Patient Reported Breast Symptoms *(Indicate all that apply.)*

L	R	Unk		Date Documented	Duration (mths)
☒	☒	☒	01=Lump or mass	____________	______
☒	☒	☒	02=Pain *Specify:*__________	____________	______
☒	☒	☒	03=Nipple discharge	____________	______
☒	☒	☒	04=Visual change	____________	______
☒	☒	☒	05=Odor	____________	______
☒	☒	☒	88=Other, *specify:*__________	____________	______
☒	☒	☒	99=Unspecified	____________	______

PATHOLOGY SUMMARIES of the specimens related to the index breast cancer.
If cytology, biopsy and surgical excision were involved, please complete for each procedure.

CYTOLOGY

(Indicate all that apply for each breast.)
Date of procedure: __ __ / __ __ / __ __ __ __

Photocopy report masking patient identifiers

L	R	Unk	Results
☒	☒	☒	00=Insufficient sample
☒	☒	☒	01=Normal cells
☒	☒	☒	02=Atypical cells
☒	☒	☒	03=Abnormal cells
☒	☒	☒	04=Malignant cells, specify type ____________
☒	☒	☒	88=Other, *specify:*____________
☒	☒	☒	99=Undetermined

(Indicate all that apply for each breast.)
Date of procedure: __ __ / __ __ / __ __ __ __

Photocopy report masking patient identifiers

L	R	Unk	Results
☒	☒	☒	00=Insufficient sample
☒	☒	☒	01=Normal cells
☒	☒	☒	02=Atypical cells
☒	☒	☒	03=Abnormal cells
☒	☒	☒	04=Malignant cells, specify type ____________
☒	☒	☒	88=Other, *specify:*____________
☒	☒	☒	99=Undetermined

(Indicate all that apply for each breast.)
Date of procedure: __ __ / __ __ / __ __ __ __

Photocopy report masking patient identifiers

L	R	Unk	Results
☒	☒	☒	00=Insufficient sample
☒	☒	☒	01=Normal cells
☒	☒	☒	02=Atypical cells
☒	☒	☒	03=Abnormal cells
☒	☒	☒	04=Malignant cells, specify type ____________
☒	☒	☒	88=Other, *specify:*____________
☒	☒	☒	99=Undetermined

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

Continued, PATHOLOGY SUMMARY of the specimens related to the index breast cancer.
If cytology, biopsy & surgical excision were involved complete for each procedure.

HISTOPATHOLOGY FROM BIOPSY (Indicate all that apply for each breast.) Date of procedure: __ __ / __ __ / __ __ __ __ Photocopy report masking patient identifiers	L	R	Unk	**Results**
	☒	☒	☒	01= Atypical hyperplasia
	☒	☒	☒	02= Ductal hyperplasia
	☒	☒	☒	03= Fibroadenoma
	☒	☒	☒	04= Intraductal carcinoma in situ (DCIS)
	☒	☒	☒	05= Lobular carcinoma in situ (CIS)
	☒	☒	☒	06= CIS not otherwise specified
	☒	☒	☒	07= Invasive ductal carcinoma (DC)
	☒	☒	☒	08= Invasive DC with DCIS
	☒	☒	☒	09= Invasive lobular carcinoma
	☒	☒	☒	10= Mucinous carcinoma
	☒	☒	☒	11= Medullary carcinoma
	☒	☒	☒	12= Papillary carcinoma
	☒	☒	☒	13= Tubular carcinoma
	☒	☒	☒	14= Adenoid cystic carcinoma
	☒	☒	☒	15= Secretory (juvenile) carcinoma
	☒	☒	☒	16= Apocrine carcioma
	☒	☒	☒	17= Paget's disease of the nipple
	☒	☒	☒	18= Invasive cancer, NOS
	☒	☒	☒	19= Cystosarcoma phyllodes
	☒	☒	☒	88= Other, *specify:*_____
	☒	☒	☒	99= Undetermined
HISTOPATHOLOGY -- SURGICAL EXICISION (Indicate all that apply for each breast.) Date of procedure: __ __ / __ __ / __ __ __ __ Photocopy report masking patient identifiers	L	R	Unk	**Results**
	☒	☒	☒	01= Atypical hyperplasia
	☒	☒	☒	02= Ductal hyperplasia
	☒	☒	☒	03= Fibroadenoma
	☒	☒	☒	04= Intraductal carcinoma in situ (DCIS)
	☒	☒	☒	05= Lobular carcinoma in situ (CIS)
	☒	☒	☒	06= CIS not otherwise specified
	☒	☒	☒	07= Invasive ductal carcinoma (DC)
	☒	☒	☒	08= Invasive DC with DCIS
	☒	☒	☒	09= Invasive lobular carcinoma
	☒	☒	☒	10= Mucinous carcinoma
	☒	☒	☒	11= Medullary carcinoma
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	☒	☒	☒	14= Adenoid cystic carcinoma
	☒	☒	☒	15= Secretory (juvenile) carcinoma
	☒	☒	☒	16= Apocrine carcioma
	☒	☒	☒	17= Paget's disease of the nipple
	☒	☒	☒	18= Invasive cancer, NOS
	☒	☒	☒	19= Cystosarcoma phyllodes
	☒	☒	☒	88= Other, *specify:*_____
	☒	☒	☒	99= Undetermined

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

STAGING (Please flag any conflicting pathology, staging, treatment or follow-up data, & discuss with investigators)

	PLEASE PHOTOCOPY PATHOLOGISTS REPORTS minus patient identifiers
Primary Tumor (T)	☒ TX Primary tumor cannot be assessed ☒ TO No evidence of primary tumor ☒ Tis Carcinoma in situ ☒ T1 Tumor ≤2 cm in greatest dimension ☒ pT1mic Microinvasion 0.1 cm or less in greatest dimension ☒ T1a Tumor >0.1 to ≤0.5 cm in greatest dimension ☒ T1b >0.5 to ≤1 cm in greatest dimension ☒ T1c >1cm to ≤2 cm in greatest dimension ☒ T2 Tumor >2 cm to 5 cm ☒ T3 Tumor >5 cm ☒ T4 Tumor of any size with direct extension to chest wall or skin ☒ T4a Extension to chest wall ☒ T4b Edema or ulceration of the skin or satellite skin nodules confined to same breast ☒ T4c Both T4a and T4b ☒ T4d Inflammatory carcinoma Paget's disease associated with a tumor is classified by size of the tumor ☒ Multifocal
Regional Lymph Nodes (N)	☒ NX Regional LN cannot be assessed (e.g., previously removed or were not sampled) ☒ N0 No regional LN metastasis ☒ N1 Spread to movable ipsilateral axillary LN(s) ☒ N2 Spread to ipsilateral axillary LN(s) fixed to one another or to other structures ☒ N3 Spread to ipsilateral internal mammary LN(s)
Pathologic Classification (pN) # LN positive _____ # LN tested _____	☒ pNX Regional LNs cannot be assessed ☒ pNO No regional LN metastasis ☒ pN1 Metastasis to movable ipsilateral axillary LN(s) ☒ pN1a Only micrometastasis (none larger than 0.2 cm) ☒ pN1bi Metastasis in 1 to 3 LNs, >0.2 to <2cm in greatest dimension ☒ pN1bii Metastasis to 4 or more LNs, >0.2 to <2cm in greatest dimension ☒ pN1biii Extension of tumor beyond capsule of a LN <2 cm in greatest dimension ☒ pN1biv Metastasis to LN ≥2 cm in dimension ☒ pN2 Metastasis to ipsilateral axillary LNs that are fixed to other LN(s) or structures ☒ pN3 Metastasis to ipsilateral internal mammary LN(s)
Distant Metastasis	☒ MX ☒ M0 ☒ M1 (includes metastasis to ipsilateral supraclavicular LN(s) If M=1, what are the number of metastatic organ sites? _____ Specify sites (which organs) _____
What was the TNM stage group, if provided?	☒ 0 (TIS) ☒ I ☒ II ☒ IIA ☒ IIB ☒ III ☒ IIIA ☒ IIIB ☒ IV ☒ Stage X (cannot be determined) ☒ Not provided
Histopathologic	☒ GX= cannot be assessed ☒ G1= well differentiated ☒ G2= moderately differentiated, ☒ G3= poorly differentiated ☒ G4= Undifferentiated ☒ G9 = Unknown

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

TREATMENT

Did the patient receive treatment?	1 = treatment carried out (mostly at HFHS) 2 = treatment primarily carried out elsewhere 3 = treatment interrupted / incomplete 4 = treatment advised but refused 5 = no treatment advised 6 = no treatment given, reasons unknown 9 = unknown whether treatment received
Was the breast cancer treated with SURGERY? **0 = no 1 = yes 9 = unknown**	If yes, what was the date? (1st if more than one) __ __/__ __/__ __ __ __ Surgery consisted of 1 = breast conserving surgery (lumpectomy, wide excision, partial mastectomy, segmental mastectomy or quadrantectomy) 2 = total mastectomy without axillary lymph node dissection 3 = modified radical mastectomy (simple mastectomy + lymph node dissection) 4 = radical mastectomy (includes pectoral muscle dissection) 5 = lumpectomy +/- node removal
Was the breast cancer treated with RADIATION?	**0 = no 1 = yes 9 = unknown** If yes, what was the start date? __ __/__ __/__ __ __ __
Was the breast cancer treated with CHEMOTHERAPY? **(other than tamoxifen)** **0 = no 1 = yes 9 = unknown**	If yes, what was the start date? __ __/__ __/__ __ __ __ What were the agents? _____ _____ _____ _____ _____ _____
Was **tamoxifen** given? **0 = no 1 = yes 9 = unknown** When was it started? __ __/__ __/__ __ __ __ For what duration was it administered? _____	
Was the breast cancer treated with HORMONE OR ENDOCRINE THERAPY <u>other than tamoxifen</u>? 0 = no 1 = yes If yes, what was the start date? __ __/__ __/__ __ __ __ **If yes, which of the following apply? (If no mention is made assume the default of "0")** **Ovarian ablation by surgery No = 0 Yes = 1** **Ovarian ablation by radiation No = 0 Yes = 1** **Luteinizing-releasing hormone antagonist No = 0 Yes = 1** **Progestins (eg. megesterol acetate or medroxyprogesterone acetate) No = 0 Yes = 1** **Estrogens No = 0 Yes = 1** **Androgens No = 0 Yes = 1** **Adrenalectomy No = 0 Yes = 1** **Hypophysectomy No = 0 Yes = 1**	

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

RESPONSE and FOLLOW-UP

Did cancer recur or spread (local or distant progression)? 0=no 1=yes 9=unknown If yes, When was it 1st noted? __ __ / __ __ / __ __ __ __ To where? _____ What was the diagnosis of recurrence/progression based on 1=pathology 2=clinical 3=both 9=not stated?
Did the patient develop one or more subsequent primary (new) breast cancers? 0=no 1=yes 9= unknown If yes, Histopathologic dx? _____ Date? __ __ / __ __ / __ __ __ __ 0=no 1=yes 9= unknown If yes, Histopathologic dx? _____ Date? __ __ / __ __ / __ __ __ __
Did the patient develop other types of primary cancer? 0=no 1=yes 9= unknown If yes, type of cancer? _____ Date? __ __ / __ __ / __ __ __ __ 0=no 1=yes 9= unknown If yes, type of cancer? _____ Date? __ __ / __ __ / __ __ __ __
Did the patient develop another type of cancer, but unknown if it is 2nd primary or metastasis? 0=no 1=yes 9= unknown If yes, type of cancer? _____ Date? __ __ / __ __ / __ __ __ __ 0=no 1=yes 9= unknown If yes, type of cancer? _____ Date? __ __ / __ __ / __ __ __ __
Do the records indicate that the patients died? 0=no 1=yes If yes, what was the death date? __ __ / __ __ / __ __ __ __ If patient died, were causes of death described? 0 = no 1 = yes If yes, what were the causes of death? _____
If the patient was alive at last contact, what was the date of the last contact? __ __ / __ __ / __ __ __ __

ALCOHOL USE (documented 5 years before to 3 years after diagnosis)

Regarding ALCOHOL consumption the records indicate the following:				
0 = Abstained from alcohol / No consumption (<1/mth) 1 = Mild use (past or present) (1-13 drinks/month) 2 = Moderate use (past or present) (4-14 drinks/wk) 3 = Past heavy use (>14 drinks/wk) 4 = Current heavy use (>14 drinks/wk) 5 = Heavy use, not otherwise specified (>14 drinks/wk) 7 = Alcohol was consumed by not quantified 8 = record shows "Ø" 9 = No alcohol data were available	Date	Date	Date	Date
	Code #	Code #	Code #	Code #

Drinks/time is a guideline. Drink ~ 1 bottle beer ~ 1 glass wine ~ 1 shot of liquor

MARIJUANA/CANNIBIS USE (documented 5 years before to 3 years after diagnosis)

Regarding MARIJUANA/CANNIBIS use the records indicate the following:				
0 = Non-user 1 = Past regular use 2 = Current regular use 3 = Both past and current use 8 = record shows "Ø" 9 = No data were available	Date	Date	Date	Date
	Code #	Code #	Code #	Code #

ILLICIT DRUG USE (documented 5 years before to 3 years after diagnosis) (e.g., cocaine, crack, heroin, or non-specified intravenous drugs, etc.)

Regarding ILLICIT DRUG use the records indicate the following:				
0 = Non-user 1 = Past regular use 2 = Current regular use 3 = Both past and current use 8 = record shows "Ø" 9 = No data were available	Date	Date	Date	Date
	Type of drug	Type of drug	Type of drug	Type of drug
	Code #	Code #	Code #	Code #

SMOKING HISTORY

Cigarette smoking data were available in the records (documented 5 years before to 3 years after diagnosis) 0=no 1=yes **?**

If yes, complete for each recording of smoking history that occurs on a different day or in a different record, even if the data appear redundant.

If smoking data were not available for the specified time period, then use available smoking data from any time period.

DATE	**"Ø"** smoking	**SMOKER** 0=Never 1=Ever	**SMOKER** 0=Never Smoker 2=Past Smoker 3=Current Smoker	**QUIT HOW LONG AGO?** (in years, use decimals if needed)	**INTENSITY** cigarettes/ day	**C. INTENSITY** packs/day	**D. DURATION** # of years smoked	**C x D = PACK-YEARS SMOKED**
__/__/____								
__/__/____								
__/__/____								
__/__/____								
__/__/____								
__/__/____								
__/__/____								
__/__/____								
__/__/____								
__/__/____								

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

Please list all medications taken by the patient for 3 years prior to the breast cancer diagnosis.
Exclude the oral contraceptives & hormone replacement therapies listed previously.

Medication	Indication why it was given	Estimate Usage 1 = Short term (< 6 months) 2 = Long term (≥ 6 months) 9 = unknown

ADDITIONAL INFORMATION / SUMMARY

If the chart information was incomplete or insufficient, check box and specify below. ☒ 01=Yes
Comments:

What is the date on the first record for this patient (not limited to the abstraction period)? __/__/__

In the 5 years prior to diagnosis, for how many years/months were records abstracted yrs __ mths __

If the records in the last 5 years had a gap > 2 year, was it because the patient

Was healthy and did not need to see a doctor? 1 = yes **(circle 1 if appropriate)**

Was being seen elsewhere? 1 = yes

Don't know the reason 1 = yes

What is the date on the last record for this patient (not limited to the abstraction period)? __/__/__

In the 3 years post diagnosis, for how many years/months were records abstracted yrs __ mths __

Record any additional comments about this case:

COMORBIDITIES

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

Please document all of the comorbidities (**Circle and indicate Yes "= 1"**) that the patient had a history of in their records from 3 years prior to diagnosis to 6 months following diagnosis or until the first treatment, which ever comes first, regardless of when the comorbidities actually occurred. The comorbidity did not have to have been present during this period, it just needed to be documented in the medical records during this time period.

If any information is given as to **when the comorbidity or sign/symptom was diagnosed or occurred** and its duration, please write it down beside its listing on the abstraction form.

For **diagnosis/occurrence**, please specify the year or date.

For **duration**, please specify the number of years/months.

The systems are listed in the following order:

(1) INFECTIOUS AND PARASITIC DISEASES

(2) PREVIOUS NEOPLASMS

(3) ENDOCRINE, NUTRITIONAL/METABOLIC DISEASES, & IMMUNITY DISORDERS

(4) DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS

(5) MENTAL DISORDERS

(6) DISEASES OF THE NERVOUS SYSTEM & SENSE ORGANS

(7) DISEASES OF THE CIRCULATORY SYSTEM

(8) DISEASES OF THE RESPIRATORY SYSTEM

(9) DISEASES OF THE DIGESTIVE SYSTEM

(10) DISEASES OF THE GENITOURINARY SYSTEM

(11) COMPLICATIONS OF PREGNANCY, CHILDBIRTH, AND THE PUERPERIUM

(12) DISEASES OF THE SKIN AND SUBCUTANEOUS TISSUE

(13) DISEASES OF MUSCULOSKELETAL SYSTEM & CONNECTIVE TISSUE

(14) CONGENITAL ANOMALIES

(15) CERTAIN CONDITIONS ORIGINATING IN THE PERINATAL PERIOD

(16) INJURY / TRAUMA & POISONING

(17) SYMPTOMS & SIGNS of the index cancer, & ILL-DEFINED CONDITIONS

APPENDIX 1 – ABSTRACTION FORM, Hormone Receptors & Breast Cancer Survival

(1) INFECTIOUS AND PARASITIC DISEASES (ICD 001-139) **No = 0 the default, YES = 1**

CM1 **Tuberculosis** Is this a recent infection (< 3 years old) or an active infection under treatment? Yes / No
CM2 **Septicemia** (except in labor)
CM3 **Bacterial infection**, unspecified site
CM4 **Mycoses**
CM5 **HIV infection / AIDS**
CM6 **Hepatitis** (infectious, not primarily alcohol-related, see #150) *Circle*: Hepatitis virus A, B, C, D, E, G, or other.
CM7 **Viral infection** (not hepatitis)
CM8 **Other infections, including parasitic**
CM9 **Sexually transmitted infections** = STD (not HIV or hepatitis)
CM10 **(Immunizations and screening for infectious disease,** If yes, specify _____)
CM248 **Gangrene**

(2) PREVIOUS NEOPLASMS (ICD 140-239)

Cancer (CA) of	A. Present No=0, Yes=1	B. Metastasis No=0, Yes=1	C. Stage	D. Histology	E. Yr of diagnosis
CM11 Head & neck					
CM12 Esophagus					
CM13 Stomach					
CM14 Colon					
CM15 Rectum & anus					
CM16 Liver & intrahepatic bile duct					
CM17 Pancreas					
CM18 Other gastrointestinal organs, peritoneum					
CM19 Bronchus, lung					
CM20 Other respiratory & intra-thoracic					
CM21 Bone & connective tissue					
CM22 Melanomas of skin					
CM23 Other non-epithelial cancer of skin					
CM24 Breast					
CM25 Uterus					
CM26 Cervix					
CM27 Ovary					
CM28 Other female genital organs					
CM29 Prostate					
CM30 Testis					
CM31 Other male genital organs					
CM32 Bladder					
CM33 Kidney and renal pelvis					
CM34 Other urinary organs					
CM35 Brain and nervous system					
CM36 Thyroid					
CM37 Hodgkin's disease					
CM38 Non-Hodgkin's lymphoma					
CM39 Leukemias					
CM40 Multiple myeloma					
CM41 Other and unspecified primary					
CM42 Secondary malignancies					
CM43 Malignant neoplasm, unspecified site					
CM44 CA, unspecified/uncertain nature or behavior					
CM45 Maintenance chemotherapy, radiotherapy		N/A	N/A	N/A	N/A
CM46 Benign neoplasm of uterus, i.e., fibroids (leiomyoma; myoma; fibromyoma)		N/A	N/A		
CM47 Other and unspecified benign neoplasm		N/A	N/A		

(3) ENDOCRINE, NUTRITIONAL/METABOLIC DISEASES, & IMMUNITY DISORDERS (ICD 240-279)

CM48 Thyroid disorders e.g., goiter, hyperthyroidism, hypothyroidism, thyroiditis. If yes, specify _____

CM49 Diabetes mellitus without complication. If yes, is it insulin-dependent? Yes / No

CM50 Diabetes mellitus with complications. If yes, specify, e.g., ketoacidosis or uncontrolled diabetes, renal, ophthalmic, neurologic, circulatory, or other/unspecified complications. _____
If yes, is it insulin-dependent? Yes / No

CM51 Other endocrine disorders, e.g., parathyroid, pituitary and its hypothalamic control, adrenal or polyglandular disorders, premature ovarian failure (menopause <40years). If yes, specify _____

CM301 Obesity / hyperalimentation documented by physician/clinician/nurse in medical records

CM52 Nutritional deficiencies (specific). If yes, specify _____

CM52B Under-nutrition/malnutrition (general/unspecified)

CM53 Disorders of lipid metabolism, e.g., hypercholesterolemia, hyperlipidemia. If yes, specify _____

CM54 Gout and other crystal arthropathies, If yes, which of the following apply?
- **CM54B** Gout, mild or not further specified
- **CM54C** Gout with nephropathy
- **CM54D** Gout with other specific manifestations
- **CM54E** Other crystal arthropathy

CM55 Fluid and electrolyte metabolic disorders, If yes, please specify on table below (Circle and indicate Yes = 1)

Water balance	**CM55B Dehydration**	**CM55C Over-hydration**
Extracellular fluid volume	**CM55D Contraction**	**CM55E Expansion / Overload**
Sodium (Na)	**CM55F Hyponatremia**	**CM55G Hypernatremia**
Potassium (K)	**CM55H Hypokalemia (hypopotassemia)**	**CM55I Hyperkalemia (hyperpotassemia)**
Calcium (Ca)	**CM55J Hypocalcemia**	**CM55K Hypercalcemia**
Phosphate (P)	**CM55L Hypophosphatemia**	**CM55M Hyperphosphatemia**
Magnesium (Mg)	**CM55N Hypomagnesemia**	**CM55O Hypermagnesemia**
Acid-Base Metabolism	**CM55P Metabolic Acidosis** **CM55R Respiratory Acidosis**	**CM55Q Metabolic Alkalosis** **CM55S Respiratory Alkalosis**
Others, specify	**CM55T** _____	

CM302 Disorder of mineral metabolism, including iron, iodine, fluorine, zinc, chromium, selenium, manganese, molybdenum, & copper. If yes, specify _____

CM56 Cystic fibrosis

CM57 Immunity disorders, If yes, specify _____

CM253 Allergic reactions

CM303 Amyloidosis

CM58 Other nutritional, endocrine, and metabolic disorders, If yes, specify _____

(4) DISEASES OF THE BLOOD AND BLOOD-FORMING ORGANS (ICD 280-289)

CM59 Deficiency and other or unspecified anemia

CM60 Acute post-hemorrhagic anemia

CM61 Sickle cell anemia

CM62 Coagulation and hemorrhagic disorders

CM63 Diseases of white blood cells

CM64 Other hematologic conditions, including spleen disorders

(5) MENTAL DISORDERS (ICD 290-319)

CM65 Mental retardation

CM66 Alcohol-related mental disorders, including acute intoxication, dependency or abuse.

CM67 Substance-related mental disorders, including barbiturate, amphetamine, hallucinogen, opioid, cocaine or other or
mixed drug dependence or abuse. Specify which drugs were used _____

CM68 Senility and organic mental disorders, including senile and arteriosclerotic dementia, Alzheimer's disease.

CM69 Affective disorders, including depressive disorder, bipolar affective disorder, manic-depressive psychosis.

CM70 Schizophrenia and related disorders
CM71 Other psychoses
CM72 Anxiety, somatoform, dissociative, and personality disorders
CM73 Preadult disorders
CM74 Other mental conditions
CM75 Personal history of mental disorder, mental & behavioral problems, observation/screening for mental condition

(6) DISEASES OF THE NERVOUS SYSTEM & SENSE ORGANS (ICD 320-389)

CENTRAL NERVOUS SYSTEM

CM76 Meningitis (except that caused by tuberculosis or sexually transmitted disease)
CM77 Encephalitis (except that caused by tuberculosis or sexually transmitted disease)
CM78 Other CNS infection and poliomyelitis If yes, specify _____
CM79 Parkinson's disease
CM80 Multiple sclerosis
CM81 Other hereditary & degenerative nervous system conditions, e.g., ALS. If yes, specify _____
CM82 Paralysis (except that secondary to cerebrovascular diseases which goes under # 113)
CM83 Epilepsy, convulsions
CM84 Headache, including migraine
CM85 Coma, stupor, and brain damage

EYE

CM86 Cataract
CM87 Retinal detachments, defects, vascular occlusion, and retinopathy
CM88 Glaucoma
CM89 Blindness and vision defects
CM90 Inflammation, infection of eye (except that caused by tuberculosis or sexually transmitted disease)
CM337 Near-sightedness (myopia), far-sightedness (hyperopia), astigmatism or needing reading glasses (presbyopia)
CM91 Other eye disorders If yes, specify _____

AUDITORY SYSTEM & OTHERS

CM92 Otitis media and related conditions
CM93 Conditions associated with dizziness or vertigo
CM94 Other ear and sense organ disorders If yes, specify _____

CM95 Other nervous system disorders If yes, specify _____

(7) DISEASES OF THE CIRCULATORY SYSTEM (ICD 390-459)

CM96 Heart valve disorders
CM97 Peri-, endo-, and myocarditis, cardiomyopathy (except that caused by tuberculosis or STD)
CM98 Essential hypertension
CM99 Hypertension with complications and secondary hypertension If yes, specify _____
CM100 Myocardial infarction How long ago was most recent MI? ____ years ____ months prior to cancer diagnosis.
CM101 Coronary atherosclerosis and other heart disease
CM102 Angina (non-specific or non-angina chest pain is coded under #322)
CM103 Pulmonary heart disease (cor pulmonale)
CM104 Other or ill-defined heart disease
CM105 Conduction disorders
CM106 Cardiac dysrhythmias / arrhythmias
CM107 Cardiac arrest or ventricular fibrillation
CM108 Congestive heart failure
CM109 Acute cerebrovascular disease
CM110 Occlusion or stenosis of precerebral arteries
CM111 Other and ill-defined cerebrovascular disease
CM112 Transient cerebral ischemia
CM113 Late effects of cerebrovascular disease, i.e., plegia or hemiplegia
CM114 Peripheral and visceral atherosclerosis
CM115 Aortic, peripheral, & visceral artery aneurysms,
CM115B If yes, where was it located? _____.

CM115C What was its size? _____ cm.
CM115D Was it surgically corrected? No = 0, Yes = 1.
CM116 Aortic and peripheral arterial embolism or thrombosis
CM117 Other circulatory disease, including hypotension
CM118 Phlebitis, thrombophlebitis and thromboembolism
CM119 Varicose veins of lower extremity
CM120 Hemorrhoids
CM121 Other diseases of veins and lymphatics

(8) DISEASES OF THE RESPIRATORY SYSTEM (ICD 460-519)

CM122 Pneumonia (except that caused by tuberculosis or sexually transmitted disease)
CM123 Influenza
CM124 Acute and chronic tonsillitis
CM125 Acute bronchitis
CM126 Other upper respiratory infections, If yes, specify _____
CM127 Chronic obstructive pulmonary disease & bronchiectasis, If yes, specify:
CM127B COPD otherwise not specified
CM127C Emphysema
CM127D Chronic bronchitis
CM127E Bronchiectasis
CM128 Asthma
CM304 Pulmonary fibrosis / interstitial lung diseases
CM129 Aspiration pneumonitis, food/vomitus
CM130 Pleurisy, pneumothorax, pulmonary collapse (atelectasis)
CM131 Respiratory failure, insufficiency, arrest (adult)
CM132 Lung disease due to external agents, including **pneumoconioses**, e.g., anthracosis, silicosis, asbestosis, berylliosis,
siderosis, stannosis, & baritosis.
CM133 Other lower respiratory disease
CM134 Other upper respiratory disease

(9) DISEASES OF THE DIGESTIVE SYSTEM (ICD 520-579)

CM135 Intestinal infection
CM136 Disorders of teeth and jaw
CM137 Diseases of mouth, excluding dental
CM138 Esophageal disorders
CM139 Gastroduodenal ulcer (except hemorrhage)
CM140 Gastritis and duodenitis
CM141 Other disorders of stomach and duodenum
CM142 Appendicitis and other appendiceal conditions
CM143 Abdominal hernia, If yes, was it accompanied by obstruction or gangrene? No = 0, Yes = 1.
CM144 Regional enteritis and ulcerative colitis, including inflammatory bowel diseases, such as Crohn's disease & ulcerative colitis.
CM145 Intestinal obstruction without hernia, e.g., paralytic ileus, impaction, adhesions. If yes, specify _____
CM146 Diverticulosis and diverticulitis
CM147 Anal and rectal conditions
CM148 Peritonitis and intestinal abscess
CM149 Biliary tract disease, e.g., cholecystitis, cholelithiasisis
CM150 Liver disease, alcohol-related
CM151 Other liver diseases, e.g., liver disease or cirrhosis without mention of alcohol, liver abscess, ascites.
CM152 Pancreatic disorders (not diabetes)
CM153 Gastrointestinal hemorrhage If yes, specify _____
CM154 Noninfectious gastroenteritis
CM155 Other gastrointestinal disorders, e.g., constipation, dysphagia. If yes, specify _____

(10) DISEASES OF THE GENITOURINARY SYSTEM (580-629)

CM156 Nephritis, nephrosis, renal sclerosis, If yes, specify _____

CM157 Acute and unspecified renal failure

CM158 Chronic renal failure

CM335 Has the patient had dialysis? If yes, earliest date _____ and last date _____

CM159 Urinary tract infections, If yes, specify if of kidney or cystitis/urethritis : _____

CM160 Calculus of urinary tract (urolithiasis) If yes, specify if of kidney or ureter or bladder : _____

What is the composition?: calcium oxalate; uric acid; cystine; struvite = magnesium ammonium phosphate, other, unknown.

CM161 Other diseases of kidney and ureters, e.g., hydronephrosis

CM162 Other diseases of bladder and urethra

CM163 Genitourinary symptoms and ill-defined conditions, e.g., hematuria, dysuria, retention of urine.

DISEASES OF THE MALE GENITAL ORGANS

CM164 Hyperplasia of prostate

CM165 Inflammatory conditions of male genital organs, If yes, specify _____

CM166 Other male genital disorders, If yes, specify _____

DISEASES OF THE FEMALE GENITAL ORGANS

CM167 Nonmalignant breast conditions

CM168 Inflammatory diseases of female pelvic organs, e.g., pelvic peritoneal adhesions, cervicitis / endocervicitis, pelvic inflammatory disease (including endometritis, salpingitis and ooporitis). If yes, specify _____

CM169 Endometriosis

CM170 Prolapse of female genital organs

CM171 Menstrual disorders

CM172 Ovarian cyst

CM173 Menopausal disorders

CM174 Female infertility

CM175 Other female genital disorders

(11) COMPLICATIONS OF PREGNANCY, CHILDBIRTH, AND THE PUERPERIUM (IDC 630-679)

CM176 Contraceptive and procreative management

CM177 Spontaneous abortion

CM178 Induced abortion

CM179 Post-abortion complications

CM180 Ectopic pregnancy

CM181 Other complications of pregnancy, e.g., genitourinary infection during pregnancy, anemia during pregnancy, mental disorder during pregnancy, missed abortion, hyperemesis gravidarum, infectious/parasitic complications in mother affecting pregnancy. If yes, specify _____

CM182 Hemorrhage during pregnancy, abruptio placenta, placenta previa

CM183 Hypertension complicating pregnancy, childbirth and the puerperium, e.g., preeclampsian/eclampsia.

CM184 Early or threatened labor

CM185 Prolonged pregnancy

CM186 Diabetes or abnormal glucose tolerance complicating pregnancy, childbirth, or the puerperium

CM187 Malposition, malpresentation

CM188 Fetopelvic disproportion, obstruction

CM189 Previous cesarean section

CM190 Fetal distress and abnormal forces of labor, e.g., fetal distress, uterine inertia, precipitate labor.

CM191 Polyhydramnios & other problems of amniotic cavity. e.g., premature rupture of membranes, infection of amnion.

CM192 Umbilical cord complication

CM193 Trauma to perineum and vulva

CM194 Forceps delivery

CM195 Other complications of birth, puerperium affecting management of mother, e.g., postpartum hemorrhage, cervical incompetence, rhesus isoimmunization, interuterine death, failed induction.

CM196 Normal pregnancy and/or delivery

(12) DISEASES OF THE SKIN AND SUBCUTANEOUS TISSUE (ICD 680-709)

CM197 Skin and subcutaneous tissue infections, e.g., cellulitis or abscess.
CM198 Other inflammatory condition of skin
CM199 Chronic ulcer of skin
CM200 Other skin disorders

(13) DISEASES OF MUSCULOSKELETAL SYSTEM & CONNECTIVE TISSUE (ICD 710-739)

CM201 Infective arthritis and osteomyelitis (except that caused by tuberculosis or sexually transmitted disease)
CM202 Rheumatoid arthritis and related disease
CM203 Osteoarthritis
CM204 Other non-traumatic joint disorders (place gout and other crystalline metabolic arthropathic disorders in #54)
CM205 Spondylosis, intervertebral disc disorders, other back problems
CM206 Osteoporosis
CM206B Osteopenia
CM207 Pathological fracture
CM208 Acquired foot deformities
CM209 Other acquired deformities
CM210 Systemic lupus erythematosus and connective tissue disorders
CM211 Other connective tissue disease
CM212 Other bone disease and musculoskeletal deformities
CM305 Limb amputation, If yes, then check if #254 applies.
CM339 Hip replacement

(14) CONGENITAL ANOMALIES (ICD 740-759)

CM213 Cardiac and circulatory congenital anomalies
CM214 Digestive congenital anomalies
CM215 Genitourinary congenital anomalies
CM216 Nervous system congenital anomalies
CM217 Other congenital anomalies

(15) CERTAIN CONDITIONS ORIGINATING IN THE PERINATAL PERIOD (ICD 760-779)

CM218 Liveborn
CM219 Short gestation, low birth weight, and fetal growth retardation
CM220 Intrauterine hypoxia and birth asphyxia
CM221 Respiratory distress syndrome
CM222 Hemolytic jaundice and perinatal jaundice
CM223 Birth trauma
CM224 Other perinatal conditions

(16) INJURY / TRAUMA & POISONING (800-999)

CM225 Joint disorders and dislocations, trauma-related
CM226 Fracture of neck of femur (hip)
CM227 Spinal cord injury
CM228 Skull and face fractures
CM229 Fracture of upper limb
CM230 Fracture of lower limb
CM231 Other fractures
CM232 Sprains and strains
CM233 Intracranial injury
CM234 Crushing injury or internal injury
CM235 Open wounds of head, neck, and trunk
CM236 Open wounds of extremities
CM237 Complication of device, implant or graft
CM238 Complications of surgical procedures or medical care
CM239 Superficial injury, contusion
CM240 Burns
CM241 Poisoning by psychotropic agents

CM242 Poisoning by other medications and drugs
CM243 Poisoning by nonmedicinal substances
CM244 Other injuries and conditions due to external causes
CM306 Gunshot injury

(17) SYMPTOMS & SIGNS of the index cancer, & ILL-DEFINED CONDITIONS (ICD 780-799)
CM307A Prior to the index cancer under study, was the patient symptomatic. No=0, Yes=1.
CM307B If symptomatic, what was the duration of symptoms? ____ months.
If symptomatic, complete the table below.

GENERAL	**CM245 Syncope, fainting** **CM249 Shock** **CM252 Fatigue and malaise, i.e., tiredness, weakness, lethargy** **CM246 Fever**, tumor-related or of unknown origin **CM308 Chills, sweats, night sweats, diaphoresis (excess or profuse perspiration)** **CM309 Weight loss (unintentional)** How many pounds were lost? ___, Over how many months? ____. Was weight loss intentional (i.e., due to dieting)? = 0, or was it disease related? = 1
GASTRO-INTESTINAL	**CM250 Nausea, vomiting, emesis** **CM310 Anorexia, loss of appetite, decreased appetite** **CM311 Heartburn** **CM336 Jaundice, icterus**
RESPIRA-TORY / CHEST	**CM312 Upper respiratory symptoms, epistaxis** **CM313 Throat symptoms, e.g.,** dysphagia, difficulty swallowing, sore throat, swollen throat, hiccups, choking sensation, hoarseness (rough or harsh quality of voice), dysphonia (any impairment of voice, a difficulty in speaking) **CM314 Cough** **CM315 Dyspnea, shortness of breath (SOB), excertional dyspnea, orthopnea** (inability to breath except in an upright position) **CM316 Wheezing** (i.e., whistling noises, high pitch, made during breathing) or **Stridor** (a harsh sound, audible without a stethoscope and predominantly inspiratory, often from obstruction) **CM317 Respiratory congestion** **CM318 Palpitations** **CM319 Hemoptysis** (coughing up blood from the respiratory tract) **CM320 Cyanosis** **CM321 Finger clubbing**
PAIN	**CM251 Abdominal pain** **CM322 Chest pain other than angina** **CM323 Pain of the back** **CM324 Pain of the shoulder** **CM325 Other pain**, e.g., arthralgia, neuralgia, pain in extremities.
NODES, MASSES, SWELLINGS	**CM247 Lymphadenitis** **CM326 Lymphadenopathy or palpable mass** or "can feel mass". **CM327 Swelling / edema**
NEURO-MUSCULAR & MENTAL	**CM328 Headache** as a presenting sign/symptom of the index cancer **CM329 Diziness** **CM330 Eye / ophthalmic symptoms & signs**, e.g., blurred vision, diplopia, photophobia. **CM331 Dysmetria** (improper measuring of distance or range of movement in muscular action) **CM338 Insomnia** **CM332 Mental changes** as a presenting sign/symptom of the index cancer **CM333 Neurologic symptoms & signs** as a presenting sign/symptom of the index cancer
OTHER	**CM334 Alopecia, hair loss**

CM254 Rehabilitation care, fitting of prostheses, and adjustment of devices

(17) UNCLASSIFIED, continued
CM259 Residual codes, unclassified
Other: Describe

APPENDIX 2 – Abstract submitted for Era of Hope Conference 2005

Comorbidity Is an Important Determinant of African American Disparity in Breast Cancer Survival

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INTRODUCTION Determinants of the poorer survival of African American compared to White breast cancer patients are not well understood. This study evaluates and quantifies the role of comorbidity in explaining this disparity.

METHODS Detailed comorbidity data were systematically abstracted directly from the medical records of a cohort of 892 breast cancer patients diagnosed in the Henry Ford Health System (HFHS) in Detroit (1985-1990). Clinicopathologic and survival data were abstracted from medical records, the HFHS and Detroit SEER Tumor Registries. In this study, data were collected on 237 comorbidities and for analysis was collapsed into 180 comorbidities in 12 comorbidity classes.

RESULTS African American race/ethnicity was associated with many predictors of reduced survival: higher stage (odds ratio (OR) $stage_{IV\ \&\ III\ vs.\ II\ \&\ I} = 1.56$, 95% CI 1.06, 2.29); adverse symptoms ($OR_{\geq 1\ vs.\ 0} = 1.29$, 95% CI 0.94, 1.76); estrogen receptor negativity ($OR_{+\ vs.\ -} = 0.67$, 95% CI 0.44, 1.01); nonreceipt of surgery ($OR_{yes\ vs.\ no} = 0.71$, 95% CI 0.37, 1.37); and older age (63.4 vs. 59.8 years, p = 0.001). Sixty-four comorbidities were classified as *adverse comorbidities* because of *a priori* reasons, significantly elevated hazard ratios (HR), or HR>1.20 regardless of statistical significance. Black patients had significantly more adverse comorbidities than White patients: median 2 versus 1; mean 2.48 versus 1.83, p<0.001).

Black patients had worse all-causes survival compared to Whites (HR = 1.341, 95% CI 1.11, 1.63). Following adjustment for comorbidity using the popular Charlson Comorbidity Index, the $HR_{Black\ vs.\ White}$ was 1.256 (95% CI 1.03, 1.52) and alternatively using a count of the comorbidities present in each of the 12 comorbidity classes under study, the $HR_{Black\ vs.\ White}$ was 1.164 (95% CI 0.95, 1.43). The Charlson Index explained 24.9% and the count of comorbidities in the 12 comorbidity classes explained 51.9% of the race/ethnic disparity in survival.

Adjusted for stage, adverse symptoms, estrogen receptor positivity, surgery, and age, the $HR_{Black\ vs.\ White}$ was 1.153 (95% CI 0.94, 1.42). Additionally adjusted for the count of adverse comorbidities in 12 classes, the $HR_{Black\ vs.\ White}$ was 1.059 (95% CI 0.89, 1.35). Thus, after adjusting for other major factors, comorbidity explained 61.4% of the remaining survival disparity. Specifically, diabetes and cardiovascular disease had major roles in explaining survival disparity.

CONCLUSION Comorbidity is an important determinant of reduced African American breast cancer survival. Optimal evaluation of comorbidity for determining breast cancer outcomes and explaining disparities awaits further research. Efforts to reduce race/ethnic disparity in breast cancer survival must consider the whole patient, including comorbidities, and not just the cancer.

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